Establishment and Validation of a Clinically Predictive Nomogram Model for Thyroid Carcinoma Patients

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Abstract

Objectives

To develop a clinically predictive nomogram model which can maximize patients' net benefit in terms of predicting the prognosis of patients with thyroid carcinoma based on the 8th edition of the AJCC Cancer Staging method.

Methods

We selected 134,962 thyroid carcinoma patients diagnosed between 2004 and 2015 from SEER database with details of the 8th edition of the AJCC Cancer Staging Manual and separated those patients into two datasets randomly. The first dataset, training set, was used to build the nomogram model accounting for 80% (94,474 cases) and the second dataset, validation set, was used for external validation accounting for 20% (40,488 cases). Then we evaluated its clinical availability by analyzing DCA (Decision Curve Analysis) performance and evaluated its accuracy by calculating AUC, C-index as well as calibration plot.

Results

Decision curve analysis showed the final prediction model could maximize patients' net benefit. In training set and validation set, Harrell's Concordance Indexes were 0.9450 and 0.9421 respectively. Both sensitivity and specificity of three predicted time points (12 Months, 36 Months and 60 Months) of two datasets were all above 0.80 except sensitivity of 60-month time point of validation set was 0.7662. AUCs of three predicted timepoints were 0.9562, 0.9273 and 0.9009 respectively for training set. Similarly, those numbers were 0.9645, 0.9329, and 0.8894 respectively for validation set. Calibration plot also showed that the nomogram model had a good calibration.

Conclusion

The final nomogram model provided with both excellent accuracy and clinical availability and should be able to predict patients' survival probability visually and accurately.

Background

The incidence of thyroid carcinoma has been rising yearly around the globe and the whole incidence of all thyroid carcinoma patients increased 3% annually according to [Hyeyeun Lim's](#) research article published on JAMA(1). Despite the increasing incidence, mortality has declined gradually due to the development of clinical treatment(2). The prognosis of thyroid carcinoma can be affected by various factors including gender, age, histology type, tumor (T-stage), node (N-stage), metastasis (M-stage), treatment strategy and so on. The current 8th edition of AJCC Cancer Staging Manual already provided with rather an effective classification, but given these specific stages as well as other factors, how do we predict the actual prognosis within certain years both visually and accurately? Which becomes imperative to build a clinical prediction model to find out which ones of those various factors are the most significant in terms of

prognosis and explain it to patients with an easily understandable way, nomogram. Nomogram is a statistical tool which can transform a clinically predictive model into a visual graph which produces a numerical probability of a certain clinical event such as death or recurrence(3). Nomogram is even more accurate and applicable in clinical prediction compared to conventional staging and has been widely used in medicine field, especially in oncology(4). Unfortunately, there hasn't been any effectively predictive nomogram models taking all useful factors (factors can maximize patients' net benefit) into consideration for thyroid carcinoma patients based on huge population data(5-7), whereas our study presented such accurate tool timely.

Materials And Methods

Study population

The design of this model was based on patients from Surveillance, Epidemiology, and End Results (SEER) Program supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS). As shown in Table 1, a total of 134,962 patients were diagnosed with thyroid carcinoma from 2004 to 2015, 32,783 of which were male and 102,179 of which were female. Each variable was stratified by gender and its percentages did not contain N/A cases. T0 was excluded from our study because there were only 290 cases identified and didn't have statistical value. Also, TX, T NOS, NX, N NOS, as well as MX were excluded because they didn't have significance for our study. All results and graphs were produced by R Project 3.6.1, Empower Stats 2.20 and IBM SPSS statistics 23.

Variable selection and univariate analysis

Gender is considered a risk factor which affects the outcome of thyroid carcinoma and it's well-known to us that female has a better chance of survival than male. The impact of gender has always been controversial as some researchers claim that there is a significant statistical difference in terms of survival between male and female(8), yet others say there is indeed a difference when gender is considered as an independent factor and this so-called significant difference will vanish in multivariate analysis(9). That's why, in our study, we analyzed gender influence in both univariate and multivariate model to explore whether this factor can be an independent predictive variable.

Age as a risk factor is introduced into the 8th edition of the AJCC Cancer Staging Manual and is divided into two groups using 55 years old as a threshold instead of the previous 45 years old in the 7th edition(10). This is very important for patients between 45-55 years old in the purpose of preventing over-staging in low-risk patients and preventing over-aggressive treatment(11).

Among the four main types of thyroid carcinoma, ATC (Anaplastic thyroid carcinoma) is the one with the rarest incidence and accounts for the majority of deaths from thyroid carcinoma despite its rare morbidity due to its malignant character(12). By contrast, PTC (Papillary thyroid carcinoma) is the commonest type with an excellent prognosis (survival rates of >95% at 25 years) and can be especially found among women(13). FTC (Follicular thyroid carcinoma) is another less common type of well-differentiated thyroid

carcinoma. MTC is an aggressive form of thyroid carcinoma causing about 8% to 15% of all thyroid cancer-related deaths(14). Different histology comes with a different prognosis and because of this difference, it's important to put histology variable into univariate analysis to see how they contribute.

There are many changes in the latest 8th edition of the AJCC cancer staging manual: For PTC, FTC and ATC, T3a is a new category and refers to a tumor >4 cm in greatest dimension limited to the thyroid gland (this number is ≥ 4 cm for MTC), T3b is a new category and is defined as a tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles), as well as level VII lymph nodes were added to N1a and MTC has been removed from above becoming a new chapter(15). Because of these changes and the latest version of SEER program didn't provide with details of 8th edition, we converted all the patients selected from 6th edition and 7th edition to 8th edition using IBM SPSS for further analysis.

There are mainly five strategies for DTC (Differentiated thyroid carcinoma) patients treatment including: TSH-suppressive therapy, ¹³¹I therapy, locoregional and adjuvant/adjunctive treatments (like surgery, radiotherapy, thermal/ethanol or cryoablation or embolization), targeted treatment, re-differentiation and other novel therapeutic approaches(16). All ATC patients fail to uptake iodine and are usually resistant to chemotherapy and the preferred strategy is surgery according to the American Thyroid Association (ATA) guidelines(17). As for patients with unresectable primary tumors, the role of surgery is to establish advantageous conditions to further perform palliative protocols(18). Different strategy should produce different prognosis, so we selected three factors including chemotherapy, ¹³¹I therapy, and surgical method to explore whether these treatment factors can be used as predictive variables.

All those factors above are associated with prognosis of thyroid carcinoma, so we evaluated influences of these factors by putting them into univariate COX regression model and Kaplan-Meier model.

Multivariate analysis and variable screening

To find out whether a certain variable still shows significantly statistical difference when other variables exist at the same time, we had to put all these variables into a COX regression model for multivariate analysis. COX model, also known as proportional hazards model, is widely used in medical researches to analyze the influences of multiple risk factors(19). In this step, we discarded those variables which may show significantly statistical difference in univariate analysis but may not in multivariate COX analysis. This COX model could produce several coefficients which later was used to develop a nomogram model.

Test of clinical use

Conventionally, there are mainly several diagnostic test indicators such as sensitivity, specificity and AUC as demonstrated below and these indicators only measure the diagnostic accuracy of the prediction model, but fail to consider the clinical availability of it. DCA (Decision Curve Analysis) is such a novel tool which can be used to evaluate whether a prediction model has clinical usage by calculating the value of net benefit within certain range of threshold probabilities(20, 21). This net benefit is produced by

comparing the difference between expected benefit and expected harm related to each proposed testing and treatment method(22). We used this tool to analyze the clinical availability of the final model.

Design and validation of predictive nomogram model

Based on cox model final results (coefficients of all variables), we then used an R package called RMS to plot a nomogram to estimate 1-year, 3-year and 5-year survival probability with a line segment(23). In order to test the accuracy of this model, we divided all patients into two groups randomly- The first dataset, training set, was used to build the nomogram model accounting for 80% (94,474 cases) and the second dataset, validation set, was used for external validation accounting for 20% (40,488 cases). The accuracy of this nomogram model can be evaluated by AUC, C-index (Harrell's Concordance Index), and calibration plot(24, 25). We used this model to predict patients' survival probability of 1-year, 3-year and 5-year time point and calculated the AUCs, C-indexes as well as calibration performances of each time point of each dataset.

Results

Univariate analysis

In univariate COX regression and Kaplan-Meier analysis (Table 2), all variables showed significantly statistical differences (P value <0.0001) although TT (total thyroidectomy) presented a slightly bigger P value (P value =0.0048). The HR (Hazard Ratio) value of female group was 0.38 (95% CI: 0.36, 0.41) compared to male group. Age group 2 had both greater HR value (10.55, 95% CI: 9.66, 11.53) and events (dead attributable to this cancer diagnosis, 2,911 cases) compared to age group 1 (586 cases). Among these four forms of thyroid carcinoma, ATC had the greatest HR value (237.99, 95% CI: 216.38, 261.75), coefficient (5.47) as well as events (736 cases) with an MST (median survival time) of 3 months. Among all T-stage groups, T4b had the greatest HR value (233.66, 95% CI: 190.75, 286.23), coefficient (5.45) with an MST of 79 months. Among N-stage groups, N1b had the greatest HR value (11.87, 95% CI: 10.36, 13.60) and coefficient (2.47) and didn't reach the MST. Between M0 and M1 groups, M1 had the greatest HR value (58.97, 95% CI: 54.94, 63.29) and coefficient (4.08) with an MST of 28 months. Patients with chemotherapy resulted in bigger HR value (44.93, 95% CI: 41.25, 48.93) and bigger coefficient (3.81) with an MST of 12 months compared to N/U (No, Unknown). Patients with ¹³¹I therapy resulted in lower HR value (0.49, 95% CI: 0.45, 0.53) and lower coefficient (-0.72) compared to N/U. As for surgical method group, the HR value and coefficient of S/N T (subtotal or near total thyroidectomy) were 2.47 (95% CI: 1.91, 3.19) and 0.90 compared to LO (Lobectomy only) and those numbers were 1.33 (95% CI: 1.09, 1.63) and 0.29 for TT (Total thyroidectomy).

Multivariate analysis

In multivariate COX regression analysis (Table 3), all variables of the final model 3 presented significantly statistical differences after variable screening procedures of model 1 and model 2. Of all levels of all variables, T4b had the greatest coefficient (3.27) and HR value (26.36, 95% CI: 19.51, 35.61). With these

coefficients, we experimentally developed two predictive models including model 3 and model 3 without ^{131}I therapy for further comparison.

Test of clinical use

Figure 1 is a comparison between model 3 and model 3 without ^{131}I therapy. It showed that using either one of these two models to predict patient's prognosis would obtain more net benefit compared to treat-all-patients group or treat-none-patients group. However, within most of the threshold probability range, DCA indicated that model 3 without ^{131}I therapy would definitely add even a lot more net benefit when comparing model 3 in terms of predicting patients' prognosis. Both prediction models were absolutely clinically useful, but model 3 without ^{131}I therapy was the best ideal one to maximize patients' net benefit.

Design of nomogram model

We transformed model 3 without ^{131}I therapy into a nomogram model (Figure 2). Each level of each variable was scored by its contribution to the final outcome and with these scores of each variable we could calculate the total points to evaluate patients' risk of death or probability of survival within certain years.

Validation of nomogram model

In training set and validation set, C-indexes were 0.9450 (95% CI: 0.9378, 0.9522) and 0.9421 (95% CI: 0.9314, 0.9528) respectively. Both sensitivity and specificity of all predicted time points (12 Months, 36 Months and 60 Months) of two datasets were all above 0.80 except sensitivity of 60-month time point of validation set was 0.7662. AUCs of three predicted time points were 0.9562, 0.9273 and 0.9009 respectively for training set. Similarly, those numbers were 0.9645, 0.9329 and 0.8894 respectively for validation set (Table 4, Figure 3). Figure 4 showed the calibration curve of each time point, X-axis stood for predicted survival probability and Y-axis stood for observed survival probability. The gray line was the ideal calibration segment. In Figure 4, all calibration curves twisted around the gray ideal one.

Discussion

In this study, we developed a nomogram model using univariate and multivariate analysis method based on 134,962 thyroid carcinoma patients' clinical data. The final nomogram model consisted of 6 variables including gender, age, histology type, T-stage, N-stage as well as M-stage. Its accuracy had been demonstrated by C-index, AUC as well as calibration plot and its clinical availability had been demonstrated by DCA. Our study showed that this nomogram model could be used to predict patients' survival probability.

The final nomogram was developed after going through 4 procedures. Firstly, we selected several positive risk factors which can worsen the final outcome such as age, gender and TNM classification and several negative treatment factors such as ^{131}I therapy and chemotherapy which can cure or alleviate the final

outcome. We could then find out whether these negative treatment factors can be used to predict patients' survival probability. Secondly, we screened out variables by putting them into univariate and multivariate analysis. In univariate analysis, all variables showed significantly statistical differences, so we then put them into multivariate analysis to see how they perform. In model 1, surgical method showed no statistical difference (P value S/N T: 0.24, TT: 0.89), which means surgical method had no effect on prognosis generally, so we removed this variable to obtain model 2. Without surgical method, chemotherapy showed no statistical difference (P value: 0.23). Likewise, we excluded chemotherapy to obtain model 3. In model 3, all variables showed significantly statistical differences. Thirdly, we used DCA to test its clinical usage and we found out that although model 3 and model 3 without ^{131}I therapy were both clinically useful, DCA suggested that model 3 without ^{131}I therapy was the best ideal one to maximize patients' net benefit in terms of predicting prognosis alone. This result also suggested that using negative treatment factors to predict patients' prognosis is inappropriate. Though ^{131}I therapy is considered to be an effective strategy, it's often used to treat DTC and is not suitable to treat other types of thyroid carcinoma(26, 27). Because of this, the final nomogram model did not contain ^{131}I therapy. Lastly, we used several indicators including C-index, AUC as well as calibration plot to evaluate its accuracy.

In univariate analysis, the HR value of female group was 0.38 compared to male group and this figure increased to 0.77 in multivariate analysis but still showed significantly statistical difference. This result indicated that gender is an applicable factor to develop a predictive model. Hwang, S.H., et al.'s study also manifested that male gender is indeed a significant independent risk factor(28). Only few studies elaborated the disparity caused by gender. Zhang, L.J., et al.'s work suggested using castrated mice model, that this difference is likely to be caused by the role of testosterone which reduces the tumor-suppressive effects of *Glipr1* and *Sfrp1* by restraining the secretion of CCL5 during cancer progression, a chemokine which activates and reinforces the antineoplastic immunologic function(29). Consequently, male patients often present advanced thyroid carcinoma(30). Several reports also manifested the higher rate of malignant thyroid nodules among male patients(31-33).

Our study showed that age variable presented a pretty higher coefficient and HR value whether in univariate analysis or multivariate analysis and the figure was even higher than T3a stage in multivariate analysis. This suggested that age is an important prognostic indicator for thyroid carcinoma. Younger patients often achieve a much better prognosis compared to older ones even they have the same degree of disease. The mechanism behind this is still unclear. One hypothesis is that older patients have a much higher level of thyroid stimulating hormone which may stimulate the mutations of TSHR (Thyroid stimulating hormone receptor) causing high rate of malignant character through two pathways including the cAMP pathway via $G_{\alpha s}$ and the Ras dependent MAPK pathway via $G_{\beta \gamma}$ and PI3K $_{\gamma}$ (34-36). Another hypothesis is that older age damages an individual's immune system like lymphocyte which can limit the invasion of malignant nodules(37).

The 8th edition of AJCC cancer staging manual subdivided N0 stage into two stages—N0a and N0b. The definition of N0a is one or more cytologically or histologically confirmed benign lymph nodes and the definition of N0b is no radiologic or clinical evidence of locoregional lymph node metastasis(38). In our

analysis, our result suggested that N0b patients indeed have a higher HR value compared to N0a (2.06, 95% CI: 1.81, 2.35 in univariate analysis, 1.53, 95% CI: 1.26, 1.85 in multivariate analysis) (Table2 and Table3). This also demonstrated the advantage of current 8th staging method which can provide clinicians with the most specific detail to treat patients with different stages.

Figure 2 also demonstrated an example we had predicted with this model. The patient's clinical stage group was IIC and his 1-year survival probability was about 30%. This predicted result was relatively close to Rao, S.N., et al.'s study (39% survival at 1 year)(39).

There are two limitations to our study. First, serological indexes were not considered currently because it's not available in the SEER database. For example, serum thyroglobulin is a necessary index which can monitor recurrence or progression of DTC and further guide the adjustment of follow-up plan and treatment strategy(40). Second, T0 stage was excluded due to the lack of cases and this made contrast less accurate compared to N-stages or M-stages. Further study will be required.

Conclusion

Generally, our study presented a nomogram model which was not only accurate but also clinically useful than conventional predictive model in terms of predicting the outcome of thyroid carcinoma. This nomogram model is also suitable to apply in other fields especially in oncology and is worth promoting vigorously.

Abbreviations

N/U, No/Unknown;

LO, Lobectomy only;

S/N T, Subtotal or near total thyroidectomy;

TT, Total thyroidectomy;

MST, Median survival time;

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets [GENERATED/ANALYZED] for this study can be found in the [Surveillance, Epidemiology, and End Results (SEER) Program] [<https://seer.cancer.gov/>]. Also, The datasets are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

RZ, ZM and KX contributed to the conception and design of the study. RZ wrote the manuscript. XL, MW, QJ, SW, XZ, XH, CH, YF and HW revised the manuscript. All authors contributed to manuscript revision, read, approved the submitted version and agreed to be accountable for all aspects of the research in ensuring the accuracy of this study. All authors have given consent to the publication of this manuscript.

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Tables

Table 1. Description of study population.			
	Male	Female	Total
Gender	32,783 (24.29%)	102,179 (75.71%)	134,962 (100%)
Age			
G1(<55years old)	16,328 (49.81%)	65,161 (63.77%)	81,489 (60.38%)
G2($\geq$ 55years old)	16,455 (50.19%)	37,018 (36.23%)	53,473 (39.62%)
Histology Type			
PTC	27,214 (88.07%)	90,593 (92.28%)	117,807 (91.27%)
FTC	2,089 (6.76%)	4,975 (5.07%)	7,064 (5.47%)
MTC	1,180 (3.82%)	1,926 (1.96%)	3,106 (2.41%)
ATC	418 (1.35%)	677 (0.69%)	1,095 (0.85%)
N/A			5,890 (N/A)
T-stage			
T1a	8,322 (27.92%)	36,004 (37.92%)	44,326 (35.53%)
T1b	5,847 (19.61%)	22,292 (23.48%)	28,139 (22.55%)
T2	5,670 (19.02%)	16,283 (17.15%)	21,953 (17.60%)
T3a	3,316 (11.12%)	5,279 (5.56%)	8,595 (6.89%)
T3b	2,421 (8.12%)	6,260 (6.59%)	8,681 (6.96%)
T4a	3,414 (11.45%)	7,409 (7.80%)	10,823 (8.67%)
T4b	821 (2.75%)	1,430 (1.51%)	2,251 (1.80%)
N/A			10,194 (N/A)
N-stage			
N0a	6,870 (23.04%)	30,506 (32.05%)	37,376 (29.90%)
N0b	14,678 (49.22%)	48,260 (50.70%)	62,938 (50.35%)
N1a	4,692 (15.73%)	11,027 (11.58%)	15,719 (12.57%)
N1b	3,581 (12.01%)	5,393 (5.67%)	8,974 (7.18%)
N/A			9,955 (N/A)
M-stage			
M0	30,317 (95.47%)	97,679 (98.23%)	127,996 (97.56%)

M1	1,437 (4.53%)	1,762 (1.77%)	3,199 (2.44%)
N/A			3,767 (N/A)
Chemotherapy			
N/U	32,171 (98.13%)	101,436 (99.27%)	133,607 (99.00%)
Yes	612 (1.87%)	743 (0.73%)	1,355 (1.00%)
¹³¹ I therapy			
N/U	15,974 (52.00%)	54,841 (55.76%)	70,815 (54.87%)
Yes	14,745 (48.00%)	43,505 (44.24%)	58,250 (45.13%)
N/A			5,897 (N/A)
Surgical Method			
LO	2,148 (7.75%)	7,205 (8.03%)	9,353 (7.96%)
S/N T	1,020 (3.68%)	3,266 (3.64%)	4,286 (3.65%)
TT	24,535 (88.56%)	79,295 (88.34%)	103,830 (88.39%)
N/A			17,493 (N/A)
G1, Group 1; G2, Group 2; N/A, Not Applicable; N/U, No/Unknown; LO, Lobectomy ONLY; S/N T, Subtotal or near total thyroidectomy; TT, Total thyroidectomy;			

Table 2. Univariate analysis.							
	Coef	SE (Coef)	HR	HR (95% CI)		P value	Events MST
				Lower	Upper		(blank/s=NR)
Gender (R=Male)						<0.0001	1,487
Female	-0.96	0.03	0.38	0.36	0.41		2,010
Age (R=G1)							586
G2	2.36	0.05	10.55	9.66	11.53		2,911
Histology Type (R=PTC)							1,435
FTC	1.06	0.07	2.88	2.52	3.29		255
MTC	2.45	0.06	11.60	10.33	13.04		352
ATC	5.47	0.05	237.99	216.38	261.75		736 3
T-stage (R=T1a)							105
T1b	0.58	0.13	1.79	1.38	2.32		124
T2	1.38	0.12	3.98	3.15	5.02		221
T3a	2.67	0.11	14.46	11.57	18.06		296
T3b	2.32	0.12	10.18	8.04	12.89		201
T4a	3.59	0.10	36.12	29.51	44.20		910
T4b	5.45	0.10	233.66	190.75	286.23		843 79
N-stage (R=N0a)							291
N0b	0.72	0.07	2.06	1.81	2.35		982
N1a	1.60	0.07	4.97	4.32	5.72		595
N1b	2.47	0.07	11.87	10.36	13.60		736
M-stage (R=M0)							1,786
M1	4.08	0.04	58.97	54.94	63.29		1,406 28

Chemotherapy (R=N/U)						2,826	
Yes	3.81	0.04	44.93	41.25	48.93	671	12
¹³¹ I therapy (R=N/U)						1,615	
Yes	-0.72	0.04	0.49	0.45	0.53	742	
Surgical Method (R=LO)						103	
S/N T	0.90	0.13	2.47	1.91	3.19	138	
TT	0.29	0.10	1.33	1.09	1.63	0.0048	1,569
Coef, Coefficient; SE, Standard Error; HR, Hazard Ratio; CI, Confidence interval; MST, Median Survival Time (Months); R, Reference; N/U, No/Unknown; LO, Lobectomy ONLY; S/N T, Subtotal or near total thyroidectomy; TT, Total thyroidectomy; NR, Not Reached;							

Table 3. Multivariate analysis and comparison of three COX models.						
	Coef	SE (Coef)	HR	HR (95% CI)		P value
				Lower	Upper	
Gender (R=M)						
Female						
Model 1	-0.32	0.07	0.73	0.63	0.84	***
Model 2	-0.26	0.06	0.77	0.68	0.87	***
Model 3	-0.27	0.06	0.77	0.68	0.87	***
Age (R=G1)						
G2						
Model 1	2.04	0.09	7.72	6.53	9.13	***
Model 2	2.03	0.08	7.63	6.54	8.91	***
Model 3	2.03	0.08	7.64	6.54	8.92	***
Histology Type (R=PTC)						
FTC						
Model 1	0.55	0.13	1.72	1.35	2.21	***
Model 2	0.44	0.11	1.55	1.24	1.94	**
Model 3	0.44	0.11	1.55	1.24	1.94	**
MTC						
Model 1	0.61	0.15	1.84	1.37	2.48	***
Model 2	0.61	0.13	1.84	1.43	2.36	***
Model 3	0.63	0.13	1.87	1.46	2.40	***
ATC						
Model 1	2.79	0.20	16.35	11.14	23.99	***
Model 2	2.77	0.14	15.96	12.07	21.09	***
Model 3	2.82	0.13	16.83	12.92	21.92	***
T-stage (R=T1a)						
T1b						
Model 1	0.34	0.18	1.40	0.98	1.99	0.06

Model 2	0.61	0.16	1.85	1.34	2.53	**
Model 3	0.61	0.16	1.85	1.35	2.54	**
T2						
Model 1	1.03	0.16	2.80	2.04	3.85	***
Model 2	1.26	0.15	3.52	2.63	4.70	***
Model 3	1.26	0.15	3.51	2.63	4.69	***
T3a						
Model 1	1.67	0.17	5.33	3.82	7.43	***
Model 2	1.95	0.15	7.00	5.19	9.45	***
Model 3	1.94	0.15	6.98	5.17	9.43	***
T3b						
Model 1	1.88	0.16	6.55	4.76	9.00	***
Model 2	2.07	0.15	7.91	5.87	10.65	***
Model 3	2.07	0.15	7.91	5.87	10.65	***
T4a						
Model 1	2.44	0.14	11.45	8.63	15.20	***
Model 2	2.71	0.13	14.98	11.53	19.45	***
Model 3	2.71	0.13	15.00	11.55	19.48	***
T4b						
Model 1	3.04	0.17	20.99	15.01	29.36	***
Model 2	3.26	0.15	26.07	19.28	35.24	***
Model 3	3.27	0.15	26.36	19.51	35.61	***
N-stage (R=N0a)						
N0b						
Model 1	0.23	0.11	1.26	1.02	1.56	0.03
Model 2	0.43	0.10	1.54	1.27	1.87	***
Model 3	0.43	0.10	1.53	1.26	1.85	***
N1a						
Model 1	0.87	0.11	2.38	1.90	2.97	***
Model 2	0.92	0.11	2.50	2.03	3.09	***

Model 3	0.91	0.11	2.48	2.01	3.05	***
N1b						
Model 1	1.06	0.12	2.88	2.30	3.62	***
Model 2	1.11	0.11	3.04	2.46	3.76	***
Model 3	1.11	0.11	3.03	2.45	3.75	***
M-stage (R=M0)						
M1						
Model 1	2.14	0.09	8.50	7.11	10.16	***
Model 2	2.13	0.08	8.42	7.17	9.90	***
Model 3	2.14	0.08	8.46	7.20	9.94	***
Chemotherapy (R=N/U)						
Yes						
Model 1	0.37	0.18	1.45	1.01	2.09	0.04
Model 2	0.17	0.14	1.18	0.90	1.55	0.23
Model 3	N/A	N/A	N/A	N/A	N/A	N/A
¹³¹ I therapy (R=N/U)						
Yes						
Model 1	-0.27	0.08	0.76	0.65	0.89	**
Model 2	-0.46	0.07	0.63	0.55	0.73	***
Model 3	-0.46	0.07	0.63	0.55	0.73	***
Surgical Method (R=LO)						
S/N T						
Model 1	0.27	0.23	1.31	0.84	2.05	0.24
Model 2	N/A	N/A	N/A	N/A	N/A	N/A
Model 3	N/A	N/A	N/A	N/A	N/A	N/A
TT						
Model 1	0.02	0.17	1.02	0.74	1.42	0.89
Model 2	N/A	N/A	N/A	N/A	N/A	N/A
Model 3	N/A	N/A	N/A	N/A	N/A	N/A

Coef, Coefficient; SE, Standard Error; HR, Hazard Ratio; CI, Confidence interval; R, Reference; M, Male; G1, Group1; G2, Group 2; N/U, No/Unknown; LO, Lobectomy ONLY; S/N T, Subtotal or near total thyroidectomy; TT, Total thyroidectomy; N/A, Not Applicable; **, = 0.0001; ***, < 0.0001;

Table 4. Accuracy evaluation of the nomogram model.

	Predicted time (months)	Sensitivity	Specificity	AUC	Harrell's C-index	C-index (95% CI)	
						Lower	Upper
Training set	12	0.8895	0.8984	0.9562	0.9450		0.9522
	36	0.8537	0.8502	0.9273		0.9378	
	60	0.8265	0.8222	0.9009			
Validation set	12	0.9284	0.8771	0.9645	0.9421		0.9528
	36	0.8585	0.8778	0.9329		0.9314	
	60	0.7662	0.8526	0.8894			
AUC, Area Under the Curve of ROC; CI, Confidence Interval;							

Figures

Figure 1

Comparison of DCA between Model 3 and Model 3 without ¹³¹I therapy. X-axis stands for threshold probability. When the diagnostic method reaches a certain value, the probability of a certain event of patient i is denoted as P_i ; When P_i reaches a certain threshold (denoted as P_t), it is defined as positive. Y-axis stands for standardized net benefit after the advantage minus the disadvantage. Net benefit is calculated by removing those false positive patients from true positive patients and then weighted by the evaluation between the disadvantage of giving up treatment and the negative influence of unnecessary treatment(41). The black horizontal line indicates that all samples are negative ($P_i < P_t$), which means none of the patients received intervention and the net benefit is 0; The gray oblique line indicates that all samples are positive and all patients received intervention.

Figure 2

A nomogram with gender, age, histology type, T-stage, N-stage and M-stage predicting the survival probability of 1-year, 3-year and 5-year time point in thyroid carcinoma. Vertical lines show a predictive example: Supposing a male patient (8 points) aged 57 (56 points) diagnosed with ATC (87 points) at T2 (37 points), N1a (22 points) and M1 (59 points) stages, his total points (269) can be projected to 1-year, 3-year and 5-year survival axis and his survival probabilities are 30%, 10% and <10% respectively.

Figure 3

Time-dependent ROC of training set and validation set. a, b and c, Training set. d, e and f, Validation set. Method = NNE (Nearest Neighbor Estimation). Bootstrap = 500. Sensitivity (True Positive Rate) = "True Positive" / "True Positive + False Negative" $\times 100\%$. Specificity (True Negative Rate) = "True Negative" / "True Negative + False Positive" $\times 100\%$.

Figure 4

Calibration plot of training set and validation set. a, b and c, Training set. d, e and f, Validation set. Bootstrap =500. X-axis, Predicted survival probability. Y-axis, Observed survival probability. Line segment at two side of intersection, 95% CI of survival probability. Gray line, Ideal (Predicted coincides exactly with observed). Black line twisting around the gray line, Difference between predicted and observed.