A Nomogram for Distinction and Potential Prediction of Lung Metastasis in Thyroid Cancer Patients

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Research

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Abstract

Background: The prognosis of thyroid cancer with lung metastasis is poor. Our aim is to develop a reliable tool to identify and predict lung metastasis (LM) in patients with thyroid cancer (TC), thereby assisting in clinical diagnosis and treatment. The aim of this study was to establish an effective Nomogram method for predicting overall survival (OS) and cancer-specific survival (CSS) in TC patients with LM.

Methods: A total of 544 patients with known distant metastatic status and epidemiological variables from the SEER database were enrolled and assigned randomly to training and validating groups in this study. Logistic regression was used to screen variables and a nomogram was established. After multivariate logistic regression age, histologic type, grade, tumor size, liver metastasis, Radiotherapy, Surgery were the important variables to construct the nomogram.

Results: The nomogram used to identify and predict the OS and CSS in TCLM patients passed the calibration and validation steps. The calibration curve and receiver operating characteristic curves (ROC) indicated the good performance of the nomogram.

Conclusions: Our nomogram is a reliable and robust tool for the identification and prediction of LM in TC patients, thus helping to better select medical examinations and optimize treatment in collaboration with medical oncologists and surgeons.

Background

According to the 2019 Cancer statistic report, thyroid carcinoma is the most common endocrine malignancy.^[1] Ninety percent of thyroid malignancies are well-differentiated forms such as papillary, follicular or medullary and their good prognosis attributed to the timely treatment and biological characteristics of the tumor.^[2] However, the lungs are the most common site of distant metastases site in DTC. Approximately 50% of patients with such metastases do not survive longer than 10 years.^[3] In 2012, Huang I-C et al. reported promising survival rates of 70.6% at 10 years and 64.9% at 15 years for patients with distant metastatic well-differentiated thyroid carcinoma.^[4] It is generally accepted that the occurrence of distant metastases in most malignancies is a factor in the low survival rate. Therefore, it is necessary to establish a survival prognostic evaluation for patients with TCLM.

Nomogram is a simple tool to construct visual models for disease prognosis in oncology.^[5] As we all know, the prognosis of TCBM is related to histological type, SREs, serum thyroglobulin (Tg), surgical resection and radiotherapy.^[6] There are no predictive models for overall survival (OS) and cancer-specific survival (CSS) in patients with TCLM. Therefore, based on the data from the Surveillance, Epidemiology, and End Results (SEER) database, our study aimed at constructing and validating a nomogram to predict 3- and 5-year OS and CSS in TCLM patients, respectively.

Methods

Study population selection

We used SEER data released in April, 2020 which covers approximately 34.6% of U.S. population and includes cases from 18 population-based registries (1975-2017). The SEER registries collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, and first course of treatment, and they follow up with patients for vital status.^[7] The analysis of the unidentified data from the SEER database was exempted from medical ethics review and didn't require informed consent. Information on site-specific metastasis was not available until after 2010, so we limited our analysis between 2010 and 2017. A total of 544 cases were found eligible for the study and establish a predictive nomogram. The patients were randomly divided into a training group (70%) and a test group (30%). In the present study, patients in the training group were used to develop the nomogram and patients in the test group were used to validate it.

Data collection

In the present study, 15 variables were used to identify the prognostic factors for TCLM, including age, sex, race, grade, histologic type, laterality, tumor size, T stage, N stage, surgery (Performed or not performed), chemotherapy (Performed or not performed) radiotherapy (Performed or not performed), liver metastasis (Yes or no), bone metastasis, and brain metastasis. In this part, CSS was the primary outcome, which was defined as the time interval between the day of diagnosis and the day of death due to cancer. The histological subtype was classified into four categories with the following ICD-O-3 codes: 8340.8341.8342.8344.8260—papillary thyroid cancer (PTC); 8330.8331.8335—follicular thyroid carcinoma (FTC); 8020.8021.8030.8032—anaplastic thyroid cancer (ATC); 8510—Medullary thyroid carcinoma (MTC).

Statistical analysis

Of the total 544 eligible TCLM patients, 374 were randomly assigned to the training cohort and the remaining 170 patients were assigned to the validation cohort to construct and validate the nomogram. All statistical analysis in our present study was conducted with SPSS 25.0 and R software (version 3.6.1). The chi-square test was used to compare the variables between the training set and the testing set. In the present study, a p-value < 0.05(two sides) was considered as statistical significance. Univariate logistic analysis was applied to identify LM-related factors. For prognostic factors, the univariate Cox regression analysis was applied to identify prognostic variables. Then, significant variables in the univariate Cox regression analysis were incorporated into the multivariate Cox regression analysis, and the independent prognostic factors of TC with LM were identified. OS and CSS were designated as the two endpoints of this study. OS and CSS were defined as the time from initial definitive diagnosis to death or to final clinical follow-up, with cause of death being all causes and TCLM, respectively.

Based on the identified independent prognostic factors nomograms were established separately for the 3-, and 5-year OS and CSS via the RMS package in R software. Meanwhile, the receiver operating characteristic (ROC) curve for the predictive nomogram was generated.^[8] The area under the curve (AUC)

was used to evaluate the discrimination of nomograms. The model was considered to function well if the AUC was between 0.5 and 1. Overall, the model was considered to have excellent performance in terms of measurement separability if the AUC was >0.75 .^[9] Moreover, the calibration curves was established for the nomogram.^[10]

Results

Population information

All included TC patients were confirmed to have LM at initial diagnosis. Table 1 shows the demographic and variables of all patients. The patients were divided into two groups processing (20–58 years and 59–90 years). Analysis of the demographic data revealed that 285 patients (52.39%) were female and the remaining 259 (47.61%) were male. As for the race of the enrolled patients, majorities were White ($n=428$ [78.68%]). Of the various histological subtype, PTC ($n=316$ [58.09%]) was the most common subtype. The most common T and N stages T3 4, respectively (85.48%) and N0 (64.89%). Of them, 87 patients (15.99%) had bone metastases, 17 (3.13%) had brain metastases, and 23 (4.23%) had liver metastases. In addition, the data highlighted that surgery and radiotherapy were the most widely accepted mode of treatment by the patients ($n=397$ [72.98%] and $n=335$ [61.58%], respectively), while chemotherapy was given in a few cases ($n=112$ [20.59%]).

Prognostic factors of OS and CSS

Table 2 shows the Univariate and multivariate Cox proportional hazards regression analysis based on all variables for OS. Statistical evaluation revealed age ($P=.003$), histologic type ($P=.001$), grade ($P<.001$), tumor size ($P=.002$), T stage ($P=.128$), combined liver metastasis ($P=.037$) radio-therapy ($P<.001$) and Surgery ($P<.001$) to be the independent risk factors. An identical method which was used to conducted for CSS identified age ($P=.001$), grade ($P=.009$), combined liver metastasis ($P=.001$), histological subtype ($P=.003$) and radio-therapy ($P=.001$) to be the independent risk factors. Statistical evaluation revealed age ($P=.032$), histologic type ($P=.012$), grade ($P=.001$), tumor size ($P=.001$), T stage ($P=.153$), combined liver metastasis ($P=.016$) radio-therapy ($P=.001$) and Surgery ($P<.001$) as the independent risk factors, as shown in Table 3.

Predictive nomogram

Based on the univariate and multivariate cox regression results, the parameters mentioned above were integrated to construct a prognostic nomogram for predicting the 3- and 5- year OS and CSS (Fig. 1)

Validation of the nomogram

The calibration curves demonstrated excellent consistency between the predicted result and the actual survival of the TCLM patients (Figs. 2 and 3). ROC analysis showed that the AUC for OS at 3-, and 5-year in the training cohort was 0.805, and 0.786 and 0.868, and 0.89 in the validation cohort, respectively (Fig.

4). The AUC for CSS at the same time points stood at 0.817 and 0.791 in the training cohort and 0.882 and 0.935 in the validation cohort (Fig. 5).

Discussion

Given the treatability and good survival rates of TC patients, the idea that it is a relatively benign form of cancer has spread widely in the medical community.^[11] In a retrospective survival analysis of 1516 papillary thyroid carcinoma cases, no difference was shown between lung metastases and multiorgan metastases. In addition, as for some practical clinical features, it was reported that age, gender, postoperative thyroglobulin (Tg) level and tumor size were risk factors for LM from TC.^[12] However, to date, no predictive model has been established, which means that the individual risk of TCLM cannot be identified by combining all independent TCLM-related predictors.

The lungs are the most common site of metastasis in Differentiated thyroid carcinomas (DTCs), followed by the bones, and rarely the brain and liver.^[13] The 10-year survival rate for patients with DTC and pulmonary metastases has been reported to be between 25% and 85%.^[14-15] Although the prognosis is extremely poor in TC patients with LM, the early detection of LM could be crucial for TC patients to receive appropriate therapy. By constructing univariate and multivariate Cox risk analysis models based on the SEER database of a large population, this study further investigated the important factors in the prognosis of TCLM patients and constructed a CSS and OS-related Nomogram model for TCLM to help identify patients at high risk of death and develop appropriate treatment strategies. In our study, the results showed that age, histologic type, grade, tumor size, liver metastasis, Radiotherapy, Surgery were the significant predictors for OS or CCS of TCLM patients. The association between these factors and LM in TC patients has been reported in previous researches.

A study by Jianing Tang et al. concluded that there were significant differences in risk factors for disease-specific survival in TC between white and black patients.^[16] However, it was not identified as an independent prognostic factor in our prognosis analysis. Age is known to be a predictive factor for recurrence and mortality in DTC.^[17] Our study also found age to be a significant predictor in TCLM. This study found histologic type of lung metastasis also to be a significant prognostic factor. The result of our study suggested that the risk of death in TCLM patients with Anaplastic was significantly higher than that in patients with other histologic type. The studies of Hu P et al.^[18] and Huang R et al.^[19] both indicated that grade was an independent predictor of malignancy, and likewise in our study. Previous studies^[20] have reported an association between tumor size level and tumor survival. Patients with larger tumor diameters were found to have a significantly lower prognosis than those with smaller tumor diameters. TCLM patients having a tumor size ≥ 81 mm indicated poor prognosis.

Liver metastasis from thyroid cancer are quite rare, with a reported frequency of 0.5%.^[21-22] However, the outcome of these patients was poor, which was the leading cause of TC-related death.^[23] OS and CSS of TCLM patients in our study showed that the presence of liver metastases was an independent risk factor

associated with prognosis. A study of the SEER database by Chenyuan Li et al.^[24] suggested that radioactive iodine (RAI) therapy in TC patients improved survival in the age <45 years group and in the well-differentiated group. The previous study is consistent with our results. Radioactive iodine (RAI) therapy plays a very important role in the treatment of TC.^[25]

Conclusion

In conclusion, our study is the first to establish and validate a relevant prognostic Nomogram model for TCLM patients, which will provide more comprehensive and accurate nomogram for predicting the 3-, and 5-year OS and CSS of TCLM patients. In addition, the establishment of the Nomogram model will help identify patients at high risk of death and help clinicians develop appropriate treatment strategies.

Abbreviations

LM: Lung metastasis; SEER: Surveillance, Epidemiology, and End Results; ROC: Receiver operating characteristic; DCA: Decision curve analysis; CSS: Cancer-specific survival; AUC: Area under the curve.

Declarations

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Authors' contributions

O ZF and Z XJ conceived of and designed the study. O ZF performed literature search. O ZF and Z XJ generated the figures and tables. O ZF analyzed the data. O ZF wrote the manuscript and Z XJ critically reviewed the manuscript. Z XJ supervised the research. All authors have read and approved the manuscript.

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Availability of data and materials

The dataset from SEER database generated and/or analyzed during the current study are available in the SEER dataset repository (<https://seer.cancer.gov/>).

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

We received permission to access the research data file in the SEER program from the National Cancer Institute, US. Approval was waived by the local ethics committee, as SEER data is publicly available and de-identified.

Consent for publication

Written informed consent for publication was obtained from all participants.

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Tables

Table 1 Clinical and pathological features of patients diagnosed as TCLM

	Total cohort (N=544)		Training cohort (N=374)		Validation cohort (N=170)	
Variables	n	%	n	%	n	%
age						
20-59	165	30.33%	116	31.02%	49	28.82%
60-90	379	69.67%	258	68.98%	121	71.18%
sex						
FEMALE	285	52.39%	197	52.67%	88	51.76%
MALE	259	47.61%	177	47.33%	82	48.24%
race						
WHITE	428	78.68%	294	78.61%	134	78.82%
BLACK	49	9.01%	33	8.82%	16	9.41%
Other	77	14.15%	47	12.57%	30	17.65%
histologic type						
Papillary	316	58.09%	210	56.15%	106	62.35%
Follicular	65	11.95%	52	13.90%	13	7.65%
Anaplastic	136	25.00%	90	24.06%	46	27.06%
Medullary	27	4.96%	22	5.88%	5	2.94%
grade						
Low (I, II)	90	16.54%	61	16.31%	29	17.06%
High (III, IV)	206	37.87%	142	37.97%	64	37.65%
Unknown	248	45.59%	171	45.72%	77	45.29%
laterality						
Left-origin of primary	17	3.13%	13	3.48%	4	2.35%
Right-origin of primary	20	3.68%	12	3.21%	8	4.71%
Bilateral	5	0.92%	3	0.80%	2	1.18%
Not a paired site	502	92.28%	346	92.51%	156	91.76%
tumor_size						
3-80	464	85.29%	318	85.03%	146	85.88%

81-160	80	14.71%	56	14.97%	24	14.12%
T stage						
T1-2	79	14.52%	45	12.03%	34	20.00%
T3-4	465	85.48%	329	87.97%	136	80.00%
N stage		0.00%		0.00%		
N0	191	35.11%	132	35.29%	59	34.71%
N1	353	64.89%	242	64.71%	111	65.29%
bone metastasis						
no	425	78.13%	283	75.67%	142	83.53%
yes	87	15.99%	86	22.99%	1	0.59%
Unknown	32	5.88%	5	1.34%	27	15.88%
brain metastasis						
no	511	93.93%	350	93.58%	161	94.71%
yes	17	3.13%	15	4.01%	2	1.18%
Unknown	16	2.94%	9	2.41%	7	4.12%
liver metastasis						
no	505	92.83%	346	92.51%	159	93.53%
yes	23	4.23%	22	5.88%	1	0.59%
Unknown	16	2.94%	6	1.60%	10	5.88%
Chemotherapy						
no/Unknown	432	79.41%	298	79.68%	134	78.82%
yes	112	20.59%	76	20.32%	36	21.18%
Radiotherapy						
no/Unknown	199	36.58%	146	39.04%	53	31.18%
yes	335	61.58%	228	60.96%	107	62.94%
Surgery						
no/Unknown	147	27.02%	101	27.01%	46	27.06%
yes	397	72.98%	273	72.99%	124	72.94%

Table 2 Univariate and multivariate Cox proportional hazards regression analysis based on all variables for OS

	HR	(95% CI)	p	HR	(95% CI)	p
age						
20-59	Reference			Reference		
60-90	1.957	1.421-2.696	<.001	1.629	1.175-2.257	0.003
Sex						
FEMALE	Reference					
MALE	1.122	0.861-1.462	0.394			
Race						
WHITE	Reference					
BLACK	0.569	0.309-1.046	0.07			
Other	1.075	0.730-1.583	0.714			
histologic type						
Papillary	Reference			Reference		
Follicular	0.946	0.601-1.491	0.812	0.58	0.352-0.955	0.032
Anaplastic	10.151	7.266-14.184	<.001	2.611	1.608-4.239	0.001
Medullary	1.769	0.988-3.167	0.055	0.836	0.434-1.610	0.592
grade						
Low (I, II)	Reference			Reference		
High (III, IV)	7.17	4.436-11.588	<.001	3.383	1.909-5.994	<.001
Unknown	1.397	0.853-2.288	0.185	1.099	0.662-1.827	0.714
laterality						
Left-origin of primary	Reference					
Right-origin of primary	0.927	0.377-2.284	0.87			
Bilateral	0.95	0.208-4.340	0.947			
Not a paired site	0.661	0.349-1.249	0.202			
tumor_size						
3-80	Reference			Reference		
81-160	2.423	1.736-3.381	<.001	1.835	1.256-2.682	0.002
T stage						

T1-2	Reference			Reference		
T3-4	2.482	1.469-4.195	0.001	1.549	0.882-2.719	0.128
N stage						
N0	Reference					
N1	1.303	0.981-1.731	0.068			
bone metastasis						
no	Reference					
yes	1.228	0.901-1.675	0.194			
Unknown	1.556	0.576-4.199	0.383			
brain metastasis						
no	Reference					
yes	1.444	0.786-2.652	0.237			
Unknown	1.482	0.697-3.150	0.306			
liver metastasis						
no	Reference			Reference		
yes	2.17	1.350-3.487	0.001	1.739	1.033-2.923	0.037
Unknown	1.075	0.399-2.896	0.886	0.724	0.260-2.014	0.536
Chemotherapy						
no/Unknown	Reference			Reference		
yes	2.527	1.873-3.411	<.001	0.873	0.608-1.253	0.46
Radiotherapy						
no/Unknown	Reference			Reference		
yes	0.453	0.347-0.591	<.001	0.529	0.393-0.714	<.001
Surgery						
no/Unknown	Reference			Reference		
yes	0.243	0.184-0.321	<.001	0.448	0.321-0.624	<.001

Table 3 Univariate and multivariate Cox proportional hazards regression analysis based on all variables for CCS

	HR	(95% CI)	p	HR	(95% CI)	p
age						
20-59	Reference			Reference		
60-90	1.864	1.311-2.651	0.001	1.489	1.035-2.142	0.032
Sex						
FEMALE	Reference					
MALE	1.147	0.848-1.552	0.372			
Race						
WHITE	Reference			Reference		
BLACK	0.466	0.218-0.997	0.049	0.813	0.374-1.769	0.602
Other	1.23	0.808-1.872	0.334	1.317	0.845-2.051	0.223
histologic type						
Papillary	Reference			Reference		
Follicular	0.984	0.594-1.629	0.949	0.483	0.273-0.854	0.012
Anaplastic	9.977	6.848- 14.538	<.001	2.368	1.370-4.094	0.002
Medullary	1.794	0.924-3.481	0.084	0.696	0.317-1.528	0.367
grade						
Low (I, II)	Reference			Reference		
High (III, IV)	7.98	4.518-14.093	<.001	3.792	1.912-7.524	0.001
Unknown	1.591	0.887-2.852	0.119	1.196	0.650-2.201	0.564
laterality						
Left-origin of primary	Reference					
Right-origin of primary	0.551	0.174-1.744	0.31			
Bilateral	0.643	0.124-3.328	0.598			
Not a paired site	0.422	0.172-1.037	0.06			
tumor_size						
3-80	Reference			Reference		
81-160	2.624	1.823-3.778	<.001	2.076	1.348-3.196	0.001
T stage						

T1-2	Reference			Reference		
T3-4	2.325	1.261-4.285	0.001	1.637	0.832-3.220	0.153
N stage						
N0	Reference					
N1	1.377	0.989- 1.917	0.058			
bone metastasis						
no	Reference					
yes	1.242	0.880-1.753	0.217			
Unknown	1.635	0.603-4.431	0.334			
brain metastasis						
no	Reference					
yes	1.28	0.599-2.731	0.524			
Unknown	1.595	0.705-3.606	0.262			
liver metastasis						
no	Reference			Reference		
yes	2.351	1.418-3.900	0.001	2.045	1.142-3.664	0.016
Unknown	1.077	0.343-3.381	0.899	1.023	0.316-3.313	0.97
Chemotherapy						
no/Unknown	Reference			Reference		
yes	2.473	1.769-3.456	<.001	0.85	0.563-1.285	0.442
Radiotherapy						
no/Unknown	Reference			Reference		
yes	0.461	0.340-0.624	<.001	0.532	0.377-0.751	0.001
Surgery						
no/Unknown	Reference			Reference		
yes	0.255	0.186-0.349	<.001	0.431	0.295-0.629	<.001

Figures

Figure 1

Nomograms predicting 3- and 5-year OS (A) and CSS (B).

Figure 2

Calibration curves. Calibration curves of the nomogram for the 3- (A), and 5-years (B) OS prediction of the training cohort, calibration curves of the nomogram for the 3- (C), and 4- years (D) OS prediction of the validation cohort.

Figure 3

Calibration curves. Calibration curves of the nomogram for the 3- (A), and 5- years (B) CCS prediction of the training cohort, calibration curves of the nomogram for the 3- (C), and 4- years (D) CCS prediction of the validation cohort.

Figure 4

ROC curves. ROC curves for predicting 3- (A), and 5-year (B) OS in the training cohort; ROC curves for predicting 3- (C), and 5-years (D) OS in the validation cohort.