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Postoperative Nomogram for Predicting Cancer-Specific Mortality in Medullary Thyroid Cancer

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Abstract

Background—Medullary thyroid cancer (MTC) is a rare thyroid cancer accounting for 5 % of all thyroid malignancies. The purpose of our study was to design a predictive nomogram for cancer-specific mortality (CSM) utilizing clinical, pathological, and biochemical variables in patients with MTC.

Methods—MTC patients managed entirely at Memorial Sloan-Kettering Cancer Center between 1986 and 2010 were identified. Patient, tumor, and treatment characteristics were recorded, and variables predictive of CSM were identified by univariable analyses. A multivariable competing risk model was then built to predict the 10-year cancer specific mortality of MTC. All predictors of interest were added in the starting full model before selection, including age, gender, pre- and postoperative serum calcitonin, pre- and postoperative CEA, RET mutation status, perivascular invasion, margin status, pathologic T status, pathologic N status, and M status. Stepdown method was used in model selection to choose predictive variables.

Results—Of 249 MTC patients, 22.5 % (56/249) died from MTC, whereas 6.4 % (16/249) died secondary to other causes. Mean follow-up period was 87 ± 67 months. The seven variables with the highest predictive accuracy for cancer specific mortality included age, gender, postoperative calcitonin, perivascular invasion, pathologic T status, pathologic N status, and M status. These variables were used to create the final nomogram. Discrimination from the final nomogram was measured at 0.77 with appropriate calibration.

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DISCLOSURES None.

Conclusions—We describe the first nomogram that estimates cause-specific mortality in individual patients with MTC. This predictive nomogram will facilitate patient counseling in terms of prognosis and subsequent clinical follow up.

Medullary thyroid cancer (MTC) is a rare subtype of thyroid malignancy derived from neuroendocrine parafollicular cells. Although 75 % are of sporadic origin, the remaining are associated with the RET proto-oncogene as part of familial or multiple endocrine neoplasia two variants. MTC is rare with an annual rate of 1,200–2,000 cases in the United States.[1,2]

Despite low incidence, MTC is responsible for a disproportionate percentage of thyroid cancer mortality: 10-year overall survival is 65 %, and drops to 40 % with the presence of distant metastases.[3] Death usually occurs due to aggressive locoregional disease with tracheoesophageal invasion or due to distant metastases to the liver, lung, or bone.[4–7]

The current method for assessing outcome is the American Joint Committee on Cancer (AJCC) TNM staging system (Supplementary Tables 1 and 2). This system stages patients from stage I to stage IV according to the T status, N status, and M status of the patient. The TNM system works effectively for a patient population but it is less useful for predicting outcome in an individual patient. In addition, it does not account for other variables that may be important for determining outcomes in individual patients. This includes patient variables, such as age, gender, and comorbidities, as well as tumor factors, such as the presence of vascular invasion (VI), margin status, and RET status. Biochemical variables that have been reported to predict outcome, such as calcitonin and carcinoembryonic antigen (CEA) levels, as well as calcitonin doubling times, also are not included in the TNM system. Calcitonin has become recognized as a highly sensitive marker; however, levels can remain detectable in many patients even after complete resection, whereas accurate doubling times in most cases require measurements over 2 years, based on American Thyroid Association management guidelines.[2,8–10]

Nomograms are statistical tools shown to predict accurately the outcome in an individual patient by utilizing multiple variables in addition to the standard TNM variables. These nomograms are created using regression analysis and expand beyond standard TNM anatomic criteria by considering previously identified factors that better approximate prognosis and outcomes.[11] As a prognostic tool, nomograms have become widely accepted in various fields due to their ability to handle complexity in a systematic, unbiased manner.[12] Well-designed nomograms have outperformed the projections of experienced clinicians and have been incorporated into clinical trial inclusion criteria and National Comprehensive Cancer Network (NCCN) guidelines.[13–15] At present, no such predictive tool applicable to individual MTC patients is available. Using clinical, pathological, and biochemical variables, we have created the first MTC nomogram that accurately predicts cause-specific mortality. Such a tool helps counsel patients by determining prognosis and the intensity of follow-up.

METHODS

Patient, Tumor, and Treatment Data

Using a DataLine search, all patients treated at Memorial Sloan-Kettering Cancer Center (MSKCC) for MTC between 1986 and 2010 were retrospectively identified. Patients with previous or synchronous thyroid malignancy, incomplete resection, or unresectable disease were excluded. A total of 249 patients were available for analysis. Pathologic staging was performed using the AJCC Staging Manual, 7th Edition.[16] Data collection were approved by the MSKCC Institutional Review Board.

Patient, tumor, and treatment characteristics were recorded for each patient from patient charts. Clinical characteristics included patient age, gender, and RET status. Tumor characteristics included tumor size, presence of extrathyroidal extension, margin status, presence of VI, pathological T status, pathological N status, and M status. Treatment characteristics included extent of thyroidectomy, extent of neck dissection, and use of postoperative radiation or chemotherapy. Biochemical variables included pre- and postoperative calcitonin levels and CEA levels. Calcitonin levels were derived via the radioimmunoassay method (normal reference value 0–50 pg/mL).[17] CEA levels were derived via the IEA Tosoh Nexia assay (Tosoh Corporation, Tokyo, Japan). The lowest calcitonin and CEA levels within the first year after surgery were recorded as the nadir. Calcitonin and CEA doubling times were calculated as previously described.[18]

Variables Predictive of 5-Year Disease-Specific Survival

The 5-year disease-specific survival (DSS) rates were calculated using the Kaplan–Meier method and analyzed via log-rank test. Variables predictive of survival were determined by univariable analysis. Statistical analysis was performed using SPSS Version 20 (IBM SPSS, Chicago, IL). Statistical significance was determined by two-sided $p < 0.05$.

Nomogram Design

A cumulative incidence plot was constructed to show the difference between death with disease and death from other causes (Supplementary Fig. 1). Follow-up length was defined as months from treatment to death or censoring. A multivariable competing risk model was then built to predict the 10-year cancer-specific mortality (CSM) of MTC. Multivariable imputation was used to impute missing values in pre- and postoperation serum calcitonin, pre- and postoperative CEA, RET mutation, VI, margin status, and pathologic T status. Log transformation was applied on continuous variables. Restricted cubic splines were used to relax the commonly assumed linear relationship between continuous predictors and the outcome. All predictors of interest were added in the starting full model before model selection, including age, gender, pre- and postoperative serum calcitonin, pre- and postoperative CEA, RET mutation, VI, margin status, M status, pathologic N status, and pathologic T status. Stepdown method was used in model selection to choose predictive variables. Of the multiple variable combinations assessed, factors with the highest predictive value were parsimoniously selected for the scale, limited by the number of events. For the final model, predictive accuracy was assessed by discrimination (the ability of a model to separate patients with different outcomes) and calibration (how far predictions are from

actual outcomes). Discrimination was measured with the concordance index, similar to the area under the receiver operating characteristic curve: values range from 0.5 (no discrimination) to 1.0 (perfect discrimination). Calibration was measured by graphically plotting the predicted against the actual probability for tertiles of the predicted probability of recurrence. R version 3.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

RESULTS

Patient, Tumor, and Treatment Characteristics

Of 249 eligible patients, 164 (66 %) were older than age 45 years (mean age 51 ± 17 years). Fifty percent were male and 40 (16 %) were positive for germline RET mutations. One hundred three (42 %) had pT3–4 tumors, 135 (56 %) had positive neck nodes, and 24 (10 %) presented with distant metastases. All patients had all gross disease removed by thyroidectomy (Table 1). Despite this, 73 (29 %) patients had close (defined as <1 mm from the inked margin) or positive microscopic margins. Ninety-four (38 %) patients had VI. The majority of patients had total thyroidectomy (93 %) and 36 (14 %) had adjuvant radiation ± chemotherapy. The mean and median preoperative calcitonin levels were 16,639 and 1,305. The mean and median postoperative nadir calcitonin levels were 1,959 and 22 during the first year of follow-up. The mean and median preoperative CEA levels were 189 and 40. The mean and median postoperative nadir CEA levels were 53 and 2.8 during the first year of follow-up.

Variables Predictive of 5-Year Disease-Specific Survival

With a mean follow-up time of 87 ± 67 months, the 5-year DSS was 85 %. Table 2 shows factors predictive of DSS by univariable analysis. Patients who were older and male had poorer outcome. As expected, patients with pT4 tumors, lateral neck disease (N1b), and distant metastases at presentation had poorer outcome (pT4 vs. pT1 59.9 % vs. 96.9 %, $p < 0.001$; pN1b vs. pN0/Nx 76.8 % vs. 93.6 %, $p < 0.001$; M1 vs. M0 55.3 % vs. 88.6 %, $p < 0.001$).

Nomogram Development and Validation

After testing multiple iterations for predictive accuracy, age, gender, postoperation serum calcitonin, VI, pathologic T status, pathologic N status, and M status were selected for the final model as having the highest predictive accuracy with the correct sign of risk for cancer specific mortality (Table 3). Internal bootstrap validation was performed to correct the overfitting bias that results from testing on the same patient population. The regression equation for 10-year CSM was given by the following equation:

$$\begin{aligned}\text{Probability of 10-year CSM}=1-(&0.9912886\\ &*\exp(0.022211219*\text{Age}\\ &+0.50780515*(\text{Sex}\\ &=\text{'Male'})+0.0413883\\ &*\text{PostOpCalcitonin}\\ &+0.87853712*(\text{PVI}\\ &=\text{'Yes'})-0.070245714\\ &*(\text{pN.A.}\\ &=\text{'N1a'})+0.7880583\\ &*(\text{pN.A.}\\ &=\text{'N1b}')+0.4827314\\ &*(\text{pT.A.}\\ &=\text{'T2}')0.85543322\\ &*(\text{pT.A.}\\ &=\text{'T3)}'+1.1115432\\ &*(\text{pT.A.}\\ &=\text{'T4}')+0.7690073*(M\\ &=\text{'M1}'))\end{aligned}$$

Discrimination and calibration were found to be excellent, with a concordance index of 0.77 (Supplementary Fig. 2). The composite nomogram based on these variables is shown in Fig. 1.

DISCUSSION

Despite an improved understanding of its pathophysiology, MTC remains a challenging disease process to manage.[19,20] Between 50 and 80 % of patients who undergo definitive resection have detectable postoperative calcitonin levels, consistent with residual disease.[4,8,10,21] Similarly, more than 50 % of patients experience biopsy-proven recurrence over 10 years, and 10 % of patients develop distant metastases despite locoregional control.[4–6,22] Patients deemed high-risk may require extensive imaging involving CT or MRI of the neck/chest/abdomen/spine, bone scans, or PET/CT to pursue biochemical recurrence that may be radiologically occult. Serial calcitonin levels to determine calcitonin doubling times may be required.[23–29] In contrast, patients considered low-risk do not require such intensive studies. A tool that can predict outcome would help with patient counseling and determine the frequency of follow-up and imaging. We describe the first nomogram for MTC that can accurately predict outcome in individual patients.

Nomograms address the complexity of balancing disparate factors via statistical modeling and quantification of risk in a way that is accessible to both patient and physician. Their systematic approach also avoids bias from an individual physician or a single aberrant clinical variable. Outside of MTC, nomograms have been demonstrated in breast and prostate cancer to be superior to conventional staging, scoring systems, and expert

opinion.[13,14,30,31] Furthermore, nomograms are arguably most valuable in situations where the potential benefit of added therapy is unclear.[31–33] Such tools are extremely useful for individualized risk stratification, helping the physician determine management where no firm guidelines may exist. Such customized planning matches the principle behind nomograms of tailoring prognosis to the patient.

We have designed a model that systematically considers multiple variables to estimate an individual MTC patient's cause-specific mortality. Our nomogram employs easily accessible clinical information, and its concordance index compares favorably with those of widely used nomograms in other fields, which have ranged between 0.64 and 0.81.[31–36] The index is especially durable given the long follow-up period in this study (mean 87 months). To illustrate the utility of the nomogram, Fig. 2a and b show two hypothetical patients. A 50-year old man with a T2N0M0 medullary cancer with no VI and postop calcitonin of 10 (Fig. 2a) has a 10-year CSM of 9 %. In contrast, a 60-year-old man with a T4N1bM0 MTC with VI and postop calcitonin level of 1,000 has a 10-year CSM of 72 % (Fig. 2b).

It is important to mention that our study has limitations. First, the nomogram was developed from the collection of retrospective data from patient charts. Therefore, it is susceptible to the biases associated with all retrospective studies. In particular, we can never fully account for selection bias associated with physician and patient factors. For example, there is variation in the extent of thyroidectomy (total versus lobectomy), extent of central neck dissection (observation, unilateral paratracheal dissection vs. bilateral paratracheal dissection), and lateral neck dissection (observation, unilateral selective neck dissection, unilateral modified radical neck dissection, bilateral neck dissection) that is highly susceptible to surgeon bias. However, our institution has a long history in thyroid cancer management and our multidisciplinary approach over the past 20 years means that such biases are minimized although not eliminated. A second limitation is in the choice of variables that we chose for the nomogram. Our nomogram did not include RET mutation status, nor calcitonin doubling times, both of which are recognized variables which predict outcome. However, it is important to note that the number of variables that can be included in a nomogram is restricted by the sample size and number of events in that sample size. In our own dataset, our analyses found that factors, such as age, gender, VI, pathological T and N classification, M status, and postoperative calcitonin conveyed the highest predictive power. Our nomogram therefore had to be constructed from the most predictive factors. Exclusion from our nomogram does not signify that factors such as RET status or calcitonin doubling time are not important.[2] We anticipate that physicians will continue to use other known variables (e.g., calcitonin doubling time, CEA) in conjunction with the nomogram, and expect that they largely corroborate this tool's output. Finally, it is important to note that our nomogram has not been validated on an external dataset. We have performed internal bootstrapping, which provides internal validation for the nomogram but, as with other widely used nomograms, future, prospective validation with larger patient populations will be necessary to further refine its fidelity and confirm its clinical relevance.[37–39]

In summary, we introduce the first nomogram to predict cause-specific mortality in individual patients with MTC. This predictive nomogram will facilitate patient counseling in terms of prognosis and subsequent clinical follow up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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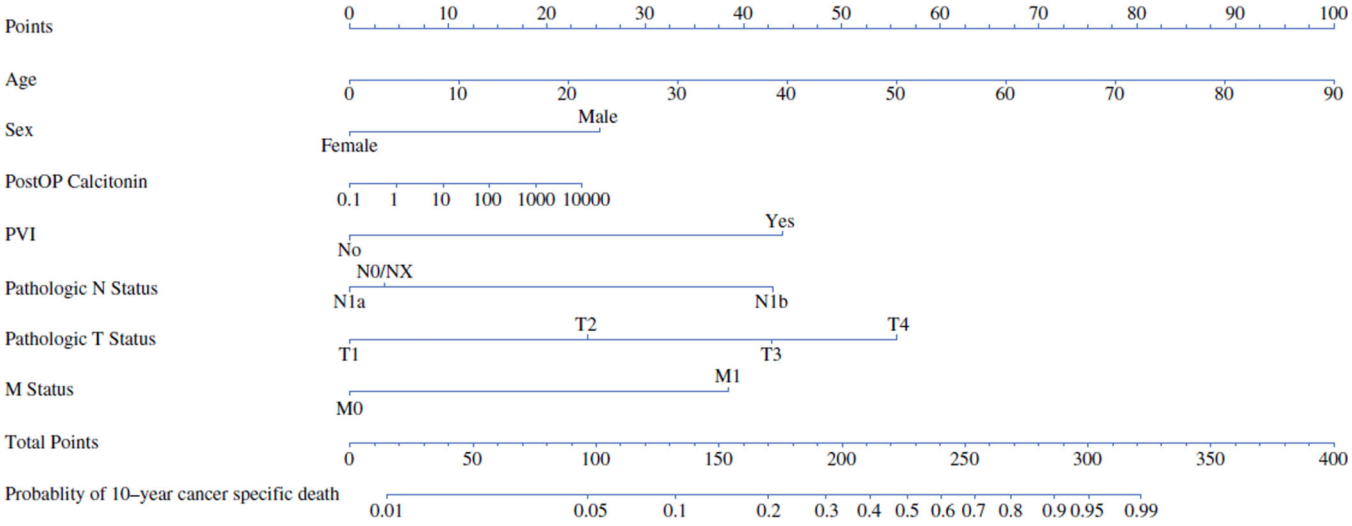

FIG. 1.
Nomogram of medullary thyroid cancer

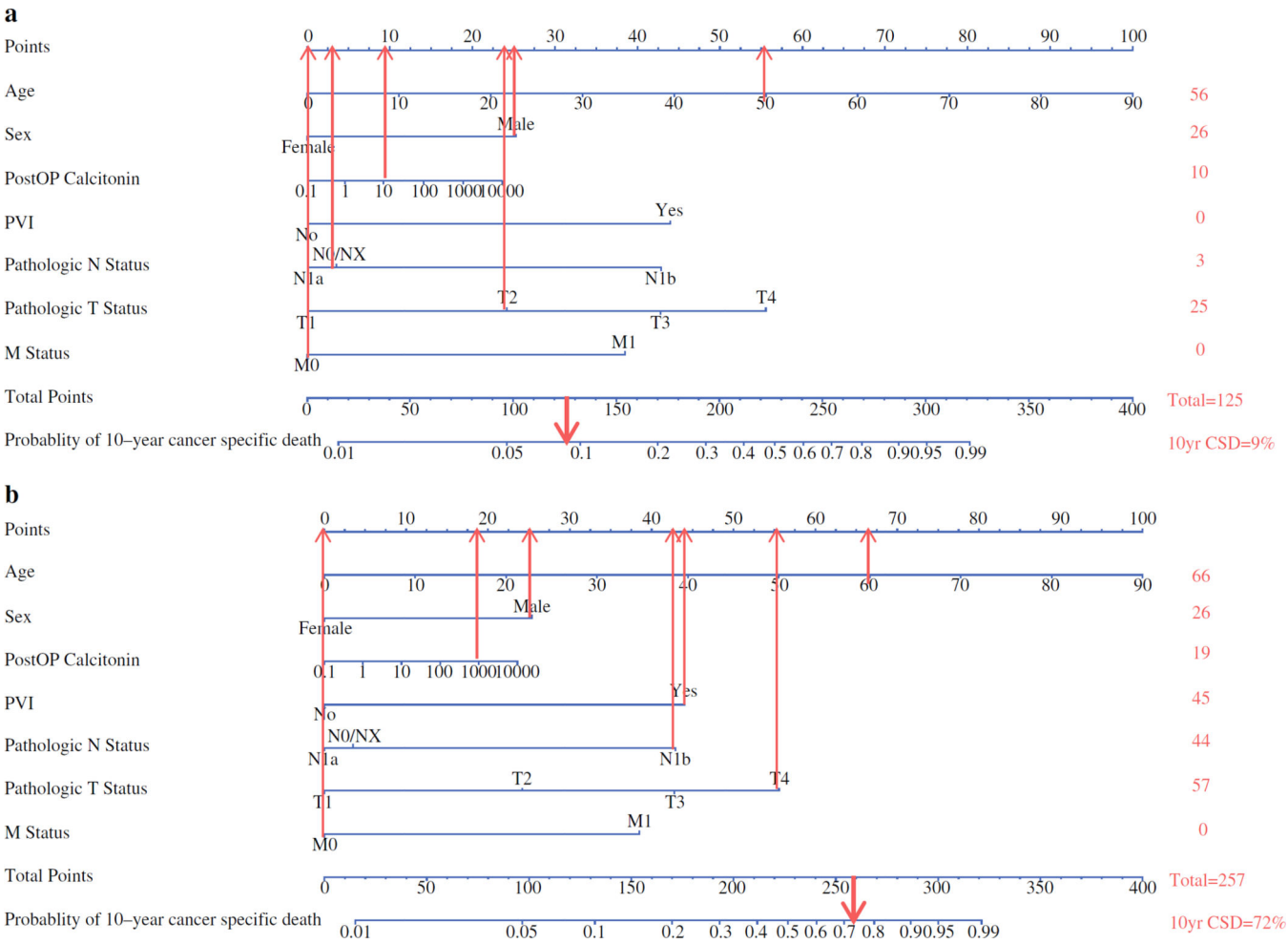

FIG. 2.

a A 50-year-old man with a T2N0M0 medullary cancer with no vascular invasion and postop calcitonin of 10 has a 10-year cancer-specific mortality of 9 %. **b** A 60-year old man with a T4N1bM0 medullary thyroid cancer with vascular invasion and postop calcitonin level of 1,000 has a 10-year cancer-specific mortality of 72 %

TABLE 1

Patient, tumor and treatment characteristics

Variable	*n* (%)
Age (year)	
<45	85 (34 %)
>45	164 (66 %)
Sex	
Female	124 (50 %)
Male	125 (50 %)
RET status	
Negative	109 (44 %)
Positive	40 (16 %)
Unknown	100 (40 %)
pT status	
pT1	88 (35 %)
pT2	39 (16 %)
pT3	61 (25 %)
pT4	42 (17 %)
Unknown	19 (8 %)
pN status	
pN0/NX	114 (46 %)
pN1a	25 (10 %)
pN1b	110 (54 %)
M status	
M0	225 (90 %)
M1	24 (10 %)
Perivascular invasion	
No	91 (36 %)
Yes	94 (38 %)
Unknown	64 (26 %)
Surgical margin	
Negative	114 (46 %)
Close	25 (10 %)
Positive	48 (19 %)
Unknown	62 (25 %)
Surgery type	
Less than total	18 (7 %)
Total thyroid	231 (93 %)
Adjuvant therapy	
None	211 (85 %)
RT and/or chemo	36 (14 %)
Unknown	2 (1 %)

TABLE 2

Univariate analysis of disease-specific survival (DSS)

Variable	5-year DSS (%)	*p* value
Age (year)		
<45	92.20	0.075
>45	81.10	
Gender		
Female	91.80	0.002
Male	79.10	
RET		
Negative	89.30	0.036
Positive	97.40	
pT status		
pT1	96.90	<0.001
pT2	88.50	
pT3	85.00	
pT4	59.90	
pN status		
pN0/NX	93.60	<0.001
pN1a	86.00	
pN1b	76.80	
M status		
M0	88.60	<0.001
M1	55.30	
Perivascular invasion		
No	98.80	<0.001
Yes	74.00	
Surgical margin		
Negative	93.40	<0.001
Close	100	
Positive	65.50	
Surgery type		
Less than total	76.40	0.45
Total thyroid	85.70	
Adjuvant therapy		
None	90.20	<0.001
RT and/or chemo	61.30	

TABLE 3

Hazard ratios for the seven variables in the nomogram

Predictor	Hazard ratio	95 % CI	*p* value
Age *	1.71	(1.07, 2.74)	0.025
Postop calcitonin **	1.54	(0.63, 3.73)	0.34
Sex—female:male	0.6	(0.33, 1.11)	0.1
PVI—yes:no	2.41	(1.14, 5.08)	0.021
pN stage			
pNO/NX	Reference		
pN1a	0.93	(0.25, 3.51)	0.14
pN1b	2.2	(0.90, 5.38)	
pT stage			
pT1	Reference		
pT2	1.62	(0.46, 5.71)	0.18
pT3	2.35	(0.95, 5.84)	
pT4	3.04	(1.11, 8.33)	
M status	2.16	(0.93, 4.99)	0.072

* Hazard ratio for age as a continuous variable is based upon the contrast of the 3rd quartile vs the 1st quartile (64 vs 40)

** Hazard ratio for postopcalcitonin as a continuous variable is based upon the contrast of the 3rd quartile vs the 1st quartile (320 vs 0)