Survival and Analysis for Mixed Medullary-Follicular Thyroid Carcinoma: based on SEER database

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Research

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Abstract

Purpose

Due to lack of proper diagnostic tools, we aimed to establish a nomogram for Mixed Medullary-Follicular Thyroid (MMFTC) and comparison with AJCC staging in prognosis.

Methods

Data regarding 203 patients with MMFTC (ICD-O-3 codes 8346, 8347) between 2000 and 2016 from The Surveillance, Epidemiology, and End Results (SEER) database. X-tile program was used to evaluate the optimal cut-off values for continuous variables. Univariate and multivariate regression analyses were performed with the Cox proportional hazards regression model to analyze the independent factors related to prognosis. Construct cancer-specific survival (CSS) and overall survival (OS) were analyzed. The resulting values were compared with the nomogram and the American Joint Committee on Cancer (AJCC) staging using C-index, verification curve, internal validation and decision curve analysis (DCA).

Results

The CSS nomogram presented the prognostic factors including year of diagnosis ($p = 0.045$), tumor size ($p = 0.003$), extrathyroidal extension ($p = 0.009$) and pN stage ($p = 0.008$), while the OS nomogram showed the prognosis factors including year of diagnosis ($p = 0.011$), age at diagnosis ($p = 0.010$), tumor size ($p = 0.013$), extrathyroidal extension ($p = 0.008$), pT2 stage ($p = 0.021$) and Radioactive implants or Radioisotopes ($p = 0.031$).The C-index, verification curve, internal validation and DCA for these nomograms showed better performance in comparisons with the AJCC staging.

Conclusion

The more appropriate and efficient therapeutic strategies were showed by the two nomograms for clinical prediction of OS and CSS in MMFTC.

Introduction

Thyroid carcinoma is the most common endocrine malignancy and more than 50,000 new cases have been diagnosed in the United States in 2019, with an increasing mortality rate (1). Thyroid carcinoma is generally classified into two histopathological groups depending on their origin: one group of Follicular cell-derived carcinoma (papillary carcinoma and follicular carcinoma) and the other group of parafollicular C cell-derived carcinoma (medullary carcinoma). Despite different origins, carcinomas of various origins can be found to coexist in the same thyroid gland; this principally involves two cases: the same thyroid gland comprises multiple carcinomas of various origins, which are independent of each other, and the single carcinoma consists of various non-homologous components, which also includes two cases: the non-homologous components of the carcinoma are adjacent to each other at their surfaces, and the non-homologous components are mixed with each other, namely, MMFTC (2).

MMFTC is an extremely rare malignant epithelial carcinoma. According to the 1988 World Health Organization Classification of tumors of endocrine organs, it can be defined as "a tumor showing the morphological feature of medullary carcinoma together with immunoreactivity for calcitonin, and the morphological features of follicular thyroid carcinoma together with immunoreactivity for thyroglobulin" (3).

At present, most studies on MMFTC were presented in the format of literature review or case report, which focused on the pathologic characteristics of the carcinoma (4, 5, 6). Therefore, it is particularly important to acquire medical data for MMFTC from large databases. The present study, with the aim of investigating the survival and analysis of prognostic factors, offers a novel perspective on MMFTC.

Materials And Methods

SEER database

The data was obtained from SEER, which has been established by the National Cancer Institute. The database represented approximately 34.6% of the US population (7). The SEER is a premier source of population-based cancer information in the US that includes therapy information, morphological features, survival data, and cancer incidence (8).

Patient selection

We selected the patients diagnosed with MMFTC (ICD-O-3 codes 8346, 8347) between 2000 and 2016 from the SEER database. The considered variables included year of diagnosis, age at diagnosis, race, sex, tumor size, extrathyroidal extension, multifocality, AJCC staging information (version 8), surgical approach, radiation, Chemotherapy, survival months and vital status. We excluded the patients with missing information, as well as those without survival time and vital status.

Statistical analysis

Descriptive statistics were used to analyze the basic characteristics of the selected patients with MMFTC. The p-value of the Categorical variables was determined by Pearson $\chi 2$ or the exact Fisher's tests. The optimal cut-off values for continuous variables (e.g., year of diagnosis, age at diagnosis, and tumor size) were determined through the use of X-tile program (Yale University, New Haven, Connecticut, USA). Univariate and multivariate regression analyses were performed utilizing the Cox proportional hazards regression model to analyze the independent factors related to prognosis. Meanwhile, 95% confidence intervals and hazard ratios were calculated and analyzed with $P < 0.05$ considered statistically significant. The above statistics analyses were conducted under SPSS version 26.0 (IBM Corp., Armonk, NY). Multivariable Cox regression was performed to draw CSS and OS nomograms, and to evaluate the accuracy of the predicted nomograms by calculating the C-index, drawing a verification curve and conducting internal validation. Finally, the clinical utility of the predictive model was evaluated by the DCA, and the DCA of the AJCC staging predictive model was drawn for comparison and the conclusion

was drawn. Nomogram, verification curve, and DCA were developed and adjusted using R version 1.2.5033 (The R Development Core Team, Vienna, Austria) in the R Studio environment.

Results

The optimal cut-off values for continuous variables

The optimal cut-off value of MMFTC patients' year of diagnosis, age at diagnosis, and tumor size was determined by the x-tile program **(figure 1)**. Based on the overall survival rate, the optimal cut-off value for the year of diagnosis was determined to be 2011, the optimal cut-off value for age and the optimal cut-off value for tumor size were determined to be 63 years and 49 mm, respectively.

Demographic and Clinicopathological Characteristics of MMFTC

A total of 203 individuals were included in this study **(table 1)**, of which, 57 (28%) were mixed medullary follicular carcinoma and 146 (72%) were mixed medullary papillary carcinoma. According to the inclusion and exclusion criteria source, patient data were obtained from the SEER database. The basic information of the patient was shown in Table 1. The person demonstrated a large age span, ranging from 18 to 92 years old, and the optimal cut-off value for age was determined to be 63 years. In this study, 81 were male (39.9%) and 116 were female (60.1%). The ratio of male to female was about 1: 1.5. The selected race was mainly Caucasian, accounting for 85.2%. Interestingly, the difference between the two types of carcinoma was apparent only in the condition that the tumor foci number ($p < 0.001$) and pT stage ($p = 0.033$) are significantly different, of which mixed medullary papillary carcinoma is mainly multifocal cancer and mixed medullary follicular carcinoma is mainly single cancer; however, there was no significant effect on survival time ($p = 0.989$). The survival time of patients was significantly different, with a large standard deviation. The median survival time was 75 months, while the shortest survival time was only 3 months.

Risk factors for survival

Based on univariate and multivariate Cox regression analysis listed in **table 2**, independent prognostic factors of cancer-specific mortality and all-cause mortality of MMFTC were determined, respectively. All-cause mortality is related to the year of diagnosis ($p = 0.011$), age at diagnosis ($p = 0.010$), tumor size ($p = 0.013$), extrathyroidal extension ($p = 0.008$), pT2 stage ($p = 0.021$) and Radioactive implants or Radioisotopes ($p = 0.031$), while tumor-specific mortality is related to the year of diagnosis ($p = 0.045$), tumor size ($p = 0.003$), extrathyroidal extension ($p = 0.009$) and pN stage ($p = 0.008$).

Construction and Validation of the Nomograms for overall survival and cancer-specific survival

The variables including year of diagnosis, age at diagnosis, tumor size, extrathyroidal extension, T stage, and radiotherapy information were adopted to construct the nomogram for OS, while the nomogram for CSS was developed based on the variables including year of diagnosis, tumor size, extrathyroidal extension and N stage. The C-indexes of the nomograms of the OS and CSS were 0.794 and 0.872,

respectively. In the internal validation cohort **(figure 3)**, the C-indexes of prediction accuracy for OS and CSS were 0.796 and 0.873, respectively. Moreover, 3, 5, and 10 years of OS and CSS calibration curves were also plotted, and it was found that the predicted results of the nomogram are consistent with the actual observed results. The results of both the quantitative and graphical evaluations show the reliability of the nomogram. Besides, on DCA **(figure 4)**, the predictive model showed great net benefit compared with AJCC 8th edition over a wider range of threshold probabilities, indicating the favorable potential clinical effect.

Discussion

At the moment, the histogenetic characteristics and pathogenetic origin of MMFTC are still obscure and have remained controversial. Several hypotheses were proposed to explain the MMFTC; one of them is the stem cell hypothesis, which assumes that follicular cells and C cells are derived from the same original stem cell and have a common proto-oncogene, and the original stem cell is capable of differentiating towards both follicular and C-cell lineage (9). The second hypothesis is a collision, which was developed on the basis of the assumption that the carcinomas occurring simultaneously are just a coincidence, which is based on the high incidence of PTC in thyroid cancer; this hypothesis was proposed specifically for the situation where two different carcinoma types collide within the same thyroid gland (10). Another is the field-effect hypothesis, assuming that a common oncogenetic stimulus triggers the neoplastic transformation of two cell-derived carcinoma (11). In some studies, the hypothesis of divergent differentiation might be involved, where the C cells adjacent to the follicular phenotype by the acquisition of additional molecular defects (12). The last hypothesis is hostage; Volante et al. (13) found that MTC is covered with hyperplastic follicles. After the normal follicular cells are encapsulated in MTC, they are stimulated and embedded by trophic factors, and the follicular cells are trapped into tumoral phenotype during the proliferation process.

In our study, we have established the nomograms to estimate the OS and CSS of extremely rare cancer. MMFTC has its unique characteristics compared to other histotypes of thyroid cancer. First, the extremely low incidence rate has led to a vague understanding of MMFTC. From 2000 to 2016, there were about 100000 cases of thyroid cancer (14), of which, MMFTC were only diagnosed in 203 cases (0.2%), which was consistent with those previously reported by Papotti et al. (15) and Kashima et al. (16). In addition, the unique pathological characteristics impede the diagnosis, leading to more significant prognostic difference. It is worth noting that the average survival time is 74.62 ± 51.41. However, so far, the previous reports on MMFTC are mostly case-series analyses and case reports, there is no established standard treatment scheme and no multicenter randomized controlled trial to guide treatment decisions. Therefore, up to now, there have been no previous studies that specifically develop MMFTC predictive model.

X-tile program was used to provide the optimal cut-off value for continuous variables that affect the prognosis of tumors (17). The optimal cut-off value for the year of diagnosis was determined to be 2011 by X-tile program. Despite continuous improvements in medical standards, the detection rate of MMFTC remains increasing. At the same time, the increase of carcinogenic factors such as chemical radiation

and environmental pollution has also had a significant impact on the survival rate of MMFTC. The age of diagnosis is an independent prognostic factor for OS by X-tile program, and we found that males have higher morbidity and mortality than females. It is considered that most male patients with thyroid cancer are often discovered in the middle or late stage (18). Meanwhile, we found some tumor-related factors, such as tumor size, extrathyroidal extension, multifocality, TNM clinical stage, and postoperative radiotherapy; these factors could serve as independent prognostic factors for OS or CSS.

Through taking into due account all the aforementioned factors, AJCC staging may not well predict MMFTC survival. Therefore, we developed a nomogram for predicting MMFTC by combining all independent prognostic factors. The reliability of the developed model can be verified by calculating the C-index, conducting internal validation, and drawing a verification curve. In the nomogram of OS, extrathyroidal extension and postoperative radiotherapy have higher risks of poor prognosis, while in the nomogram of CSS, tumor size and lymph node metastasis have higher risks of poor prognosis, indicating that postoperative risk increases when the tumor enlarges and breaks through the thyroid capsule and extrathyroidal extension occurs (19), and lymph node metastasis is the most common form of thyroid cancer metastasis. When the above occurs, combined thyroidectomy with radioactive implants or radioisotopes may improve the efficacy of treatment for MMFTC. Meanwhile, we found that the independent prognostic factors of CSS are significantly less than OS, and age as an independent prognostic factor only appears in the nomogram of OS. As such, elderly patients who suffer from thyroid cancer are likely to be more susceptible to other infectious diseases.

In this study, some potential limitations should still be highlighted and discussed herein. The main limitation results from the SEER database. Specifically, the lack of recurrence information will result in a positive offset in the evaluation of OS and CSS; moreover, the prediction accuracy is also limited owing to the lack of molecular biomarkers (such as BRAF mutation, RAS mutation, etc.), calcitonin, and other related variable information. In addition, it is worth noting that the data for rare diseases are considerably sparse and a validation cohort is absent in our study (20). To minimize the effect of this bias, we used all available data and comprehensively analyzed the relevant variables. However, compared with the AJCC staging, the nomogram based on independent prognostic factors shows satisfactory prediction accuracy. Besides, DCA demonstrates the excellent clinical applicability of the predictive nomogram in our study. Analogously, several studies on different types of thyroid cancer have utilized DCA to verify the benefits and clinical utility of the predictive capacity of the established models (21, 22, 23). These studies suggest that the nomogram model is a superior risk prediction method in comparison with AJCC staging in terms of both OS and CSS, allowing clinicians to develop more appropriate and efficient therapeutic strategies for MMFTC patients.

Conclusions

Although MSTC is an extremely rare disease in multiple countries, the incidence of thyroid cancer have shown increasing trends across in the recent years, more and more patients cases of thyroid cancer being described in MSTC. Meanwhile, with further exploration of the molecular mechanism of MMFTC and

development of clinical technology, the means of tumor treatment are continuously improved and perfected. We are confident of that, in the next few years, more accurate therapeutic methods will be developed for MMFTC and can achieve superior clinical outcomes.

Abbreviations

SEER: the Surveillance, Epidemiology, and End Results;MMFTC：Mixed Medullary-Follicular Thyroid；AJCC：American Joint Committee on Cancer；CSS：Construct cancer-specific survival； OS：overall survival；DCA：decision curve analysis；USA：the United States；TNM：Tumor Node Metastasis；MSTC：mixed subtype thyroid cancer.

Declarations

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Authors’contributions

WZ conceived, designed and wrote the initial draft of the manuscript. WZ, WB, MX and CZD performed the statistical analyses. TW, XHQ and WZ reviewed, revised and approved the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The article uses the seer database, which is publicly available free of charge, so ethical exemptions are available at the First Medical Center of Chinese People’s Liberation Army General Hospital.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA-Cancer J Clin. 2019;69:7–34.
2. Maruna Pavel,Duskova Jaroslava,Limanova Zdena. et al. Mixed medullary and follicular cell carcinoma of the thyroid in a 71-year-old man with history of malignant melanoma.[. J]Med Sci Monit. 2008;14:CS31–6.
3. Hedinger C,Williams ED,Sobin LH.Histological typing of thyroid tumours. Second edition. No. 11 in: International Histological Classification of Tumours, World Health Organization. Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong: Springer-Verlag, 1988.
4. Seki T, Kameyama K, Hayashi H. Composite Metastatic Carcinoma in Lymph Nodes of Patients with Concurrent Medullary and Papillary Thyroid Carcinoma : A Report of Two Cases[J]. Endocr Pathol. 2004;15(1):83–8.
5. Bhatnagar P, Bhatnagar A, Kishan S, et al. Unusual Widespread Metastatic Presentation of Mixed Medullary–Follicular Thyroid Carcinoma[J]. Clin Nucl Med. 2004;29(5):303–5.
6. Goyal R, Nada R, Rao KLN, et al. Mixed medullary and follicular cell carcinoma of the thyroid with lymph node metastasis in a 7-year-old child[J]. Pathol Int. 2006;56(2):84–8.
7. Liu Y, Wang Y, Zhao K, et al. Lymph node metastasis in young and middle-aged papillary thyroid carcinoma patients: a SEER-based cohort study.[. J]BMC Cancer. 2020;20:181.
8. Wang S,Xiong Yiquan,Zhao Qiuyang et al. Columnar cell papillary thyroid carcinoma prognosis: findings from the SEER database using propensity score matching analysis.[J].Am J Transl Res, 2019, 11: 6262–6270.
9. Goyal R, Nada R, Rao KLN, et al. Mixed medullary and follicular cell carcinoma of the thyroid with lymph node metastasis in a 7-year-old child[J]. Pathol Int. 2006;56(2):84–8.
10. Maruna Pavel,Duskova Jaroslava,Limanova Zdena. et al. Mixed medullary and follicular cell carcinoma of the thyroid in a 71-year-old man with history of malignant melanoma.[. J]Med Sci Monit. 2008;14:CS31–6.
11. Seki T, Kameyama K, Hayashi H. Composite Metastatic Carcinoma in Lymph Nodes of Patients with Concurrent Medullary and Papillary Thyroid Carcinoma : A Report of Two Cases[J]. Endocr Pathol. 2004;15(1):83–8.
12. Younes N, Shomaf M, Al Hassan L. Simultaneous medullary and papillary thyroid carcinoma with lymph node metastasis in the same patient: case report and review of the literature[J]. Asian J Surg. 2005;28(3):223–6.
13. Volante M, Papotti M, Roth J, et al. Mixed medullary-follicular thyroid carcinoma. Molecular evidence for a dual origin of tumor components[J]. Am J Pathol,1999,155(5): 1499–1509.
14. Liu C, Zhao Q, Li Z, et al. Mixed subtype thyroid cancer: A surveillance, epidemiology, and end results database analysis[J]. Oncotarget. 2017;8(49):86556–65.
15. Papotti M, Negro F, Carney JA, Bussolati G, Lloyd RV. Mixed medullary-follicular carcino- ma of the thyroid. A morphological, immuno- histochemical and in situ hybridization analysis of 11 cases. Virchows Arch. 1997;430:397–405.

16. Kashima K, Yokoyama S, Inoue S, et al. Mixed medullary and follicular carcinoma of the thyroid: report of two cases with an immunohistochemical study.[J].Acta Pathol. Jpn. 1993;43:428–33.
17. Camp RL. X-Tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res. 2004;10:7252–9. doi:10.1158/1078-0432.CCR-04-0713.
18. Sipos JA,Mazzaferri EL.Thyroid cancer epidemiology and prognostic variables.[J].Clin Oncol (R Coll Radiol), 2010, 22: 395–404. DOI:10.1016/j.clon.2010.05.004.
19. Shaha Ashok R. Clinical significance of extrathyroidal extension according to size of papillary thyroid carcinoma.[J]. Eur J Surg Oncol. 2018;44:1669–70.
20. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31:1188–95.
21. Wen Qian,Yu Yong,Yang. Jin, et al. Development and Validation of a Nomogram for Predicting Survival in Patients with Thyroid Cancer[J]Med Sci Monit, 2019, 25: 5561–71.
22. Zhang Jianxing,Meng
Chen L,Zhang Jianxing,Meng Lingcui, et al. A new ultrasound nomogram for differentiating benign and malignant thyroid nodules.[J].Clin. Endocrinol (Oxf), 2019, 90: 351–9.
23. Lu Si,Zhao Rongjie,Ni Yeqin, et al. Development and validation of a nomogram for preoperative prediction of cervical lymph node involvement in thyroid microcarcinoma.[J].Aging (Albany NY), 2020, 12: 4896–4906.

Tables

Table 1: Demographic and Clinicopathological Characteristics of MMFTC

Variable	Histological types				
	Mixed medullary papillary carcinoma (n=146)	Mixed medullary follicular carcinoma (n=57)	x2 value	P value	MMFTC (203)
Year of diagnosis			2.143	0.143	
2000-2011	89(61.0%)	41(71.9%)			130(64%)
2012-2016	57(39.0%)	16(28.1%)			73(36%)
Age at diagnosis (year)			1.208	0.272	
< 64	99(67.8%)	34(59.6%)			133(66%)
≥ 64	47(32.2%)	23(40.4%)			70(34.5%)
Sex			0.056	0.812	
Male	59(40.4%)	22(38.6%)			81(39.9%)
Female	87(59.6%)	35(61.4%)			122(60.1%)
Race			0.780	0.677	
White	126(86.3%)	47(82.5%)			173(85.2%)
Black	8(5.5%)	5(8.8%)			13(6.4%)
Other	12(8.2%)	5(8.8%)			17(8.4%)
Tumor size (mm)			0.001	0.975	
< 50	127(87%)	50(87.7%)			177(87.2%)
≥ 50	15(10.3%)	6(10.5%)			21(10.3%)
Unknown	4(2.7%)	1(1.8%)			5(2.5%)
Extrathyroidal extension			0.005	0.943	
None	121(82.9%)	47(82.5%)			168(82.8%)
Yes	25(17.1%)	10(17.5%)			35(17.2%)
Multifocality			23.163	< 0.001	
None	31(21.2%)	29(50.9%)			60(29.6%)
Yes	106(72.6%)	19(33.3%)			125(61.6%)
Unknown	9(6.2%)	9(15.8%)			18(8.9%)
T stage (8th)			8.705	0.033	
T1	71(48.6%)	22(38.6%)			93(45.8%)
T2	31(21.2%)	17(29.8%)			48(23.6%)
T3	35(24.0%)	10(17.5%)			45(22.2%)
T4	6(4.1%)	8(14.0%)			14(6.9%)
Unknown	3(2.1%)	0			3(1.5%)
N stage (8th)			0.439	0.508	
N0	98(67.1%)	41(71.9%)			129(68.5%)
N1	48(32.9%)	16(28.1%)			64(31.5%)
M stage (8th)			0.823	0.364	
M0	136(93.2%)	55(96.5%)			191(94.2%)
M1	10(6.8%)	2(3.5%)			12(5.9%)
Surgery			2.326	0.127	
Thyroidectomy only	45(30.8%)	24(42.1%)			69(34.0%)
Thyroidectomy + lymph node dissection	101(69.2%)	33(57.9%)			134(69.0%)
Radiation			1.368	0.562	
None or refused	102(69.9%)	37(64.9%)			139(68.5%)
Beam radiation	5(3.4%)	4(7.0%)			9(4.4%)
Radioactive implants or Radioisotopes	39(26.7%)	16(28.1%)			55(27.1%)
Chemotherapy			0.399	0.528	
None or unknown	141(96.6%)	56(98.2%)			197(97.0%)
Yes	5(3.4%)	1(1.8%)			6(3.0%)
Survival months (month)	72.39±51.64	80.33±50.83	0.291	0.989	74.62±51.41

Table 2 : Risk factors for survival: outcome of MMFTC cancer specific mortality and all-cause mortality

Variable	Thyroid Cancer specific mortality				All cause mortality			
	Univariate Cox regression		Multivariate Cox regression		Univariate Cox regression		Multivariate Cox regression	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Year of diagnosis								
2000-2011	1		1		1		1	
2012-2016	1.897(0.540-6.664)	0.318	5.297(1.034-27.131)	0.045	2,335(0.879-6.198)	0.089	4.398(1.402-13.792	0.011
Age at diagnosis (year)								
< 64	1		1		1		1	
≥ 64	0.934(0.361-2.418)	0.888	0.564(0.113-2.817)	0.485	2.412(1.320-4.409)	0.004	2.714(1.275-5.777)	0.010
Sex								
Male	1		1		1		1	
Female	0.564(0.239-1.331)	0.191	0.609(0.193-1.922)	0.397	0.666(0.365-1.213)	0.184	0.702(0.318-1.551)	0.382
Race								
White	1		1		1		1	
Black	0.601(0.081-4.478)	0.619	0.247(0.024-2.596)	0.244	0.961(0.296-3.113)	0.946	0.608(0.141-2.621)	0.505
Other	-	0.980	-	0.982	0.489(0.118-2.032)	0.325	0.816(0.184-3.620)	0.789
Tumor size (mm)								
< 50	1		1		1		1	
≥ 50	6.154(2.508-15.097)	< 0.001	22.061(2.835-171.656)	0.003	3.584(1.733-7.414)	0.001	4.689(1.387-15.850)	0.013
Extrathyroidal extension								
None	1		1		1		1	
Yes	7.159(3.007-17.043)	< 0.001	9.895(1.754-55.827)	0.009	4.082(2.222-7.502)	< 0.001	5.921(1.601-21.901)	0.008
Multifocality								
None	1		1		1		1	
Yes	0.992(0.372-2.644)	0.987	0.662(0.154-2.851)	0.579	0.896(0.453-1.771)	0.752	0.765(0.323-1.809)	0.542
T stage (8th)								
T1	1		1		1		1	
T2	12.532(1.509-104.110)	0.019	8.845(0.953-82.077)	0.055	2.461(1.063-5.700)	0.036	3.035(1.182-7.793)	0.021
T3	15.174(1.865-123.430)	0.011	1.292(0.087-19.189)	0.853	2.792(1.203-6.478)	0.017	0.685(0.177-2.653)	0.584
T4	40.641(4.995-330.673)	0.001	1.070(0.045-25.347)	0.966	5.847(2.427-14.090)	< 0.001	0.867(0.111-6.747)	0.892
N stage (8th)								
N0	1		1		1		1	
N1	8.476(3.101-23.167)	< 0.001	40.734(2.616-634.407)	0.008	2.450(1.353-4.438)	0.003	2.816(0.989-8.022)	0.053
M stage (8th)								
M0	1		1		1		1	
M1	12.710(5.065-31.893)	< 0.001	1.141(0.168-7.750)	0.892	7.327(3.329-16.126)	< 0.001	1.549(0.318-7.548)	0.588
Surgery								
Thyroidectomy only	1		1		1		1	
Thyroidectomy + lymph node dissection	2.095(0.766-5.732)	0.15	0.121(0.009-1.618)	0.111	1.033(0.561-1.903)	0.916	0.484(0.182-1.285)	0.145
Radiation								
None or refused	1		1		1		1	
Beam radiation	6.478(2.120-19.790)	0.001	1.349(0.254-7.156)	0.725	3.045(1.073-8.640)	0.036	0.679(0.118-3.895)	0.664
Radioactive implants or Radioisotopes	0.514(0.148-1.790)	0.296	0.349(0.075-1.616)	0.178	0.452(0.199-1.028)	0.058	0.325(0.117-0.903)	0.031

Figures

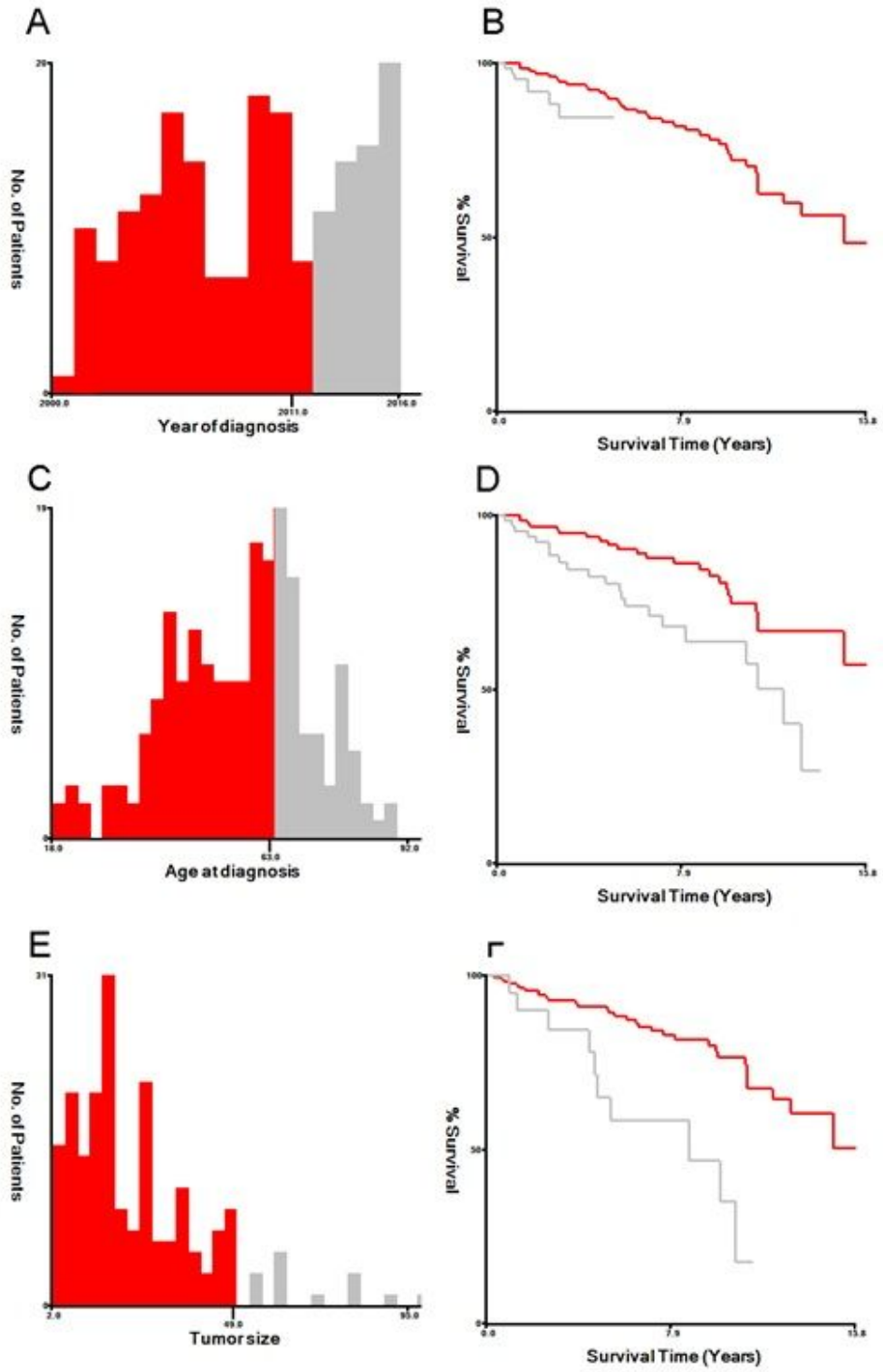

Figure 1

Identification of optimal cut-off values of year of diagnosis (A,B), age at diagnosis (C,D), and tumor size (E,F) by X-tile program. The optimal cut-off value for the year of diagnosis was determined to be 2011, the optimal cut-off value for age was determined to be 63 years and the optimal cut-off value for tumor size was determined to be 49 mm .

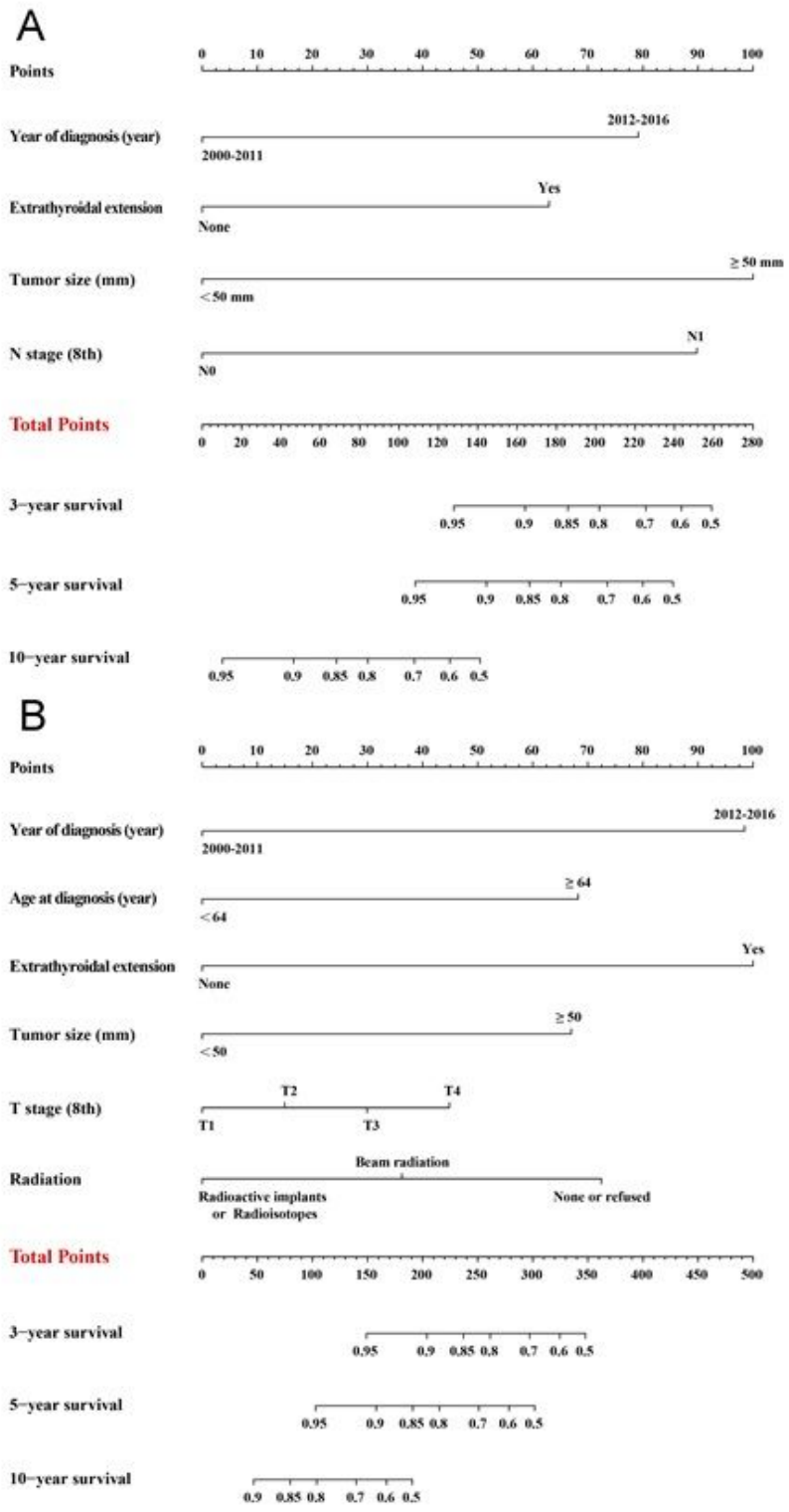

Figure 2

Nomograms to predict 3-, 5- and 10- year of cancer specific survival (A) and overall survival (B) for patients with MMFTC.

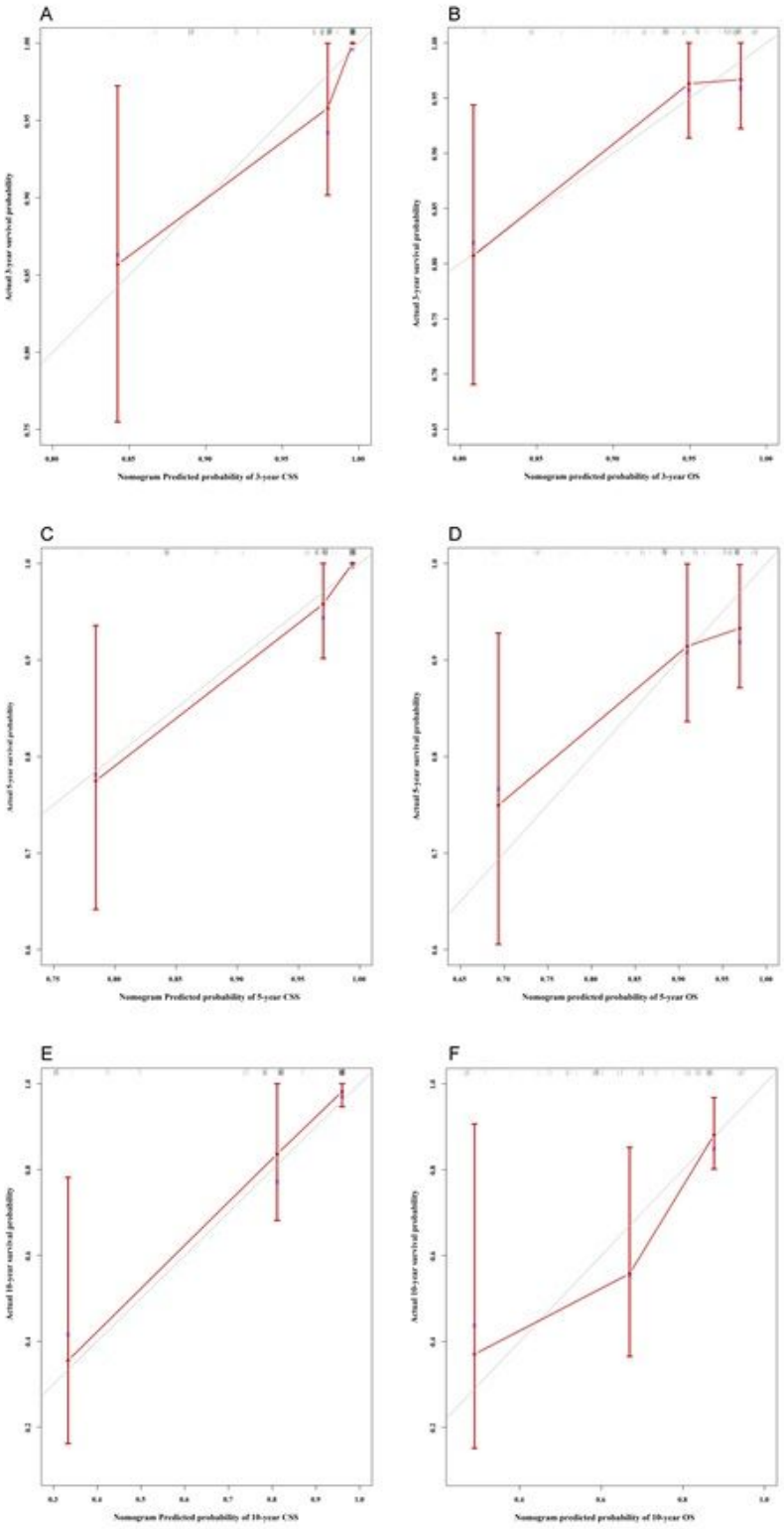

Figure 3

Internal verification plots of 3-(A), 5-(C) and 10-year (E) cancer-specific survival nomogram verification curves; 3-(B), 5-(D) and 10-year (F) overall survival nomogram verification curves

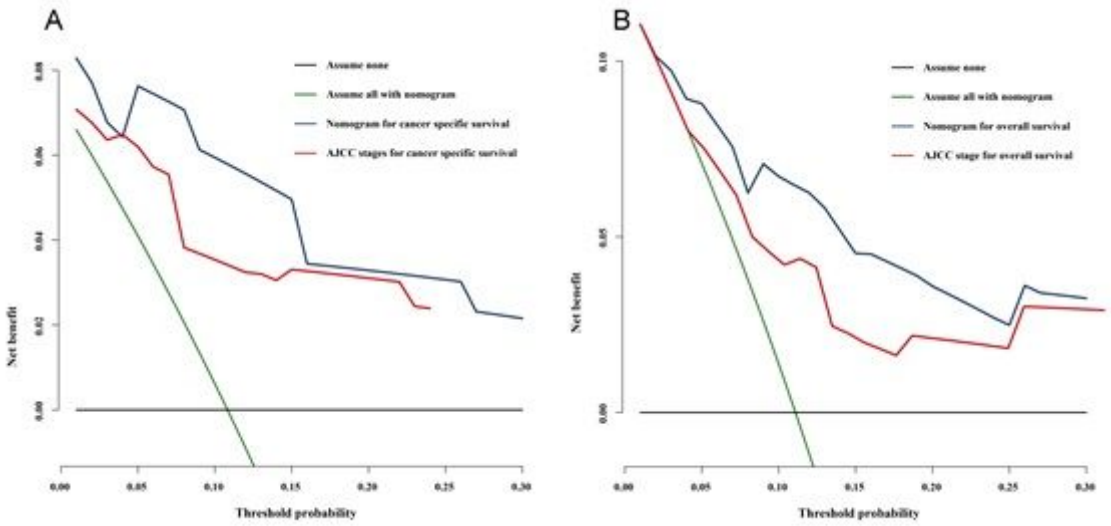

Figure 4

Decision curve analysis of nomograms and AJCC staging system for predicting cancer specific survival (A) and overall survival (B).