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Analysis

A nomogram to predict cancer-specific mortality in adult patients with malignant meningioma: a competing risk analysis

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Received: 16 March 2024 / Accepted: 22 August 2024
Published online: 31 August 2024
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Abstract

Background Comprehensive investigations of the prognosis factors and treatment strategies with adjustment of competing causes of death for patients with malignant meningioma (MM) is still lacking.

Patient and method The surveillance, Epidemiology, and End Results (SEER) database were used to include adult patients with this rare disease between 2004 and 2018. The probability of MM-caused mortality (MMCM) and non-MM-caused mortality (non-MMCM) were presented by cumulative incidence function curves. Then, the association between variates with non-MMCM was evaluated by the cox proportional hazard model, and the prognostic factors of MMCM were identified by Fine-Gray competing risk regression model. Furthermore, a nomogram was developed to predict the 1-year, 2-year, and 5-year MMCM and the performance was tested by a time-dependent area under the receiver operating characteristic (ROC) curve and calibration.

Result 577 patients were included, with a median age of 62 (18–100) years old and a median overall survival time of 36 (0–176) months. The percentage of non-MMCM was 15.4% (n = 89) in the entire population and 21.7% (n = 54) in elderly patients. The multivariable Cox proportional hazard regression model revealed that older age and other tumor(s) before or after MM had an independently significant association with higher non-MMCM. After adjustment of competing causes of death, the multivariable Fine-gray regression model identified age group ≥ 65 year, tumor size > 5.3 cm, recurrent MM, and histologic type 9530/3 (Meningioma, malignant) had an independently significant association with higher MMCM. Compared with gross total (GTR) of tumor, subtotal resection of tumor (HR 1.66, 95%CI 1.08–2.56, P = 0.02), partial resection of lobe (HR 2.26, 95%CI 1.32–3.87, P = 0.003), and gross total resection of lobe (HR 1.69, 95%CI 1.12–2.51, P = 0.01) had an independently significant association with higher MMCM.

Conclusion The competing risk nomogram including age group, tumor size, initial status, histologic type, and extent of resection is discriminative and clinically useful. This study emphasized the importance of the GTR of tumor in the treatment of MM patients, which had a significantly lower incidence of MMCM compared with biopsy, STR of tumor, partial resection of lobe, and GTR of lobe.

Hongfu Zhang and Jing Li have contributed equally to this work.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12672-024-01263-y.

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Keywords Malignant meningioma · Gross total resection · Competing risks · SEER · Nomogram

1 Introduction

Meningioma is the most common intracranial tumor, accounting for 38.3% of all brain tumors [1]. According to the 2021 WHO classification of tumors of the central nervous system, meningiomas were classified as benign (WHO grade 1), atypical (WHO grade 2), and anaplastic (malignant) (WHO grade 3) [2]. Compared with non-malignant meningioma (non-MM), malignant meningioma (MM) has a lower incidence but much worse survival. According to the most recent report from the Central Brain Tumor Registry of the United States (CBTRUS), MM composes 1.04% of all meningiomas with an incidence of 0.09 per 100,000, and the ten-year relative survival rates for non-MM and MM were 87.4% and 59.6% respectively [1]. The European Association of Neuro-Oncology (EANO) guidelines suggested surgical resection as radical as possible followed by postoperative radiotherapy (PORT) for the MM treatment [3]. However, the evidence and recommendation level were not high, and more research based on a large patient cohort is needed. Given the low incidence of MM, few studies have reported the prognostic factors and treatment measures with strong evidence. In most published studies, a small number of MM patients were analyzed together with atypical meningioma [4–6]. And to the best of our knowledge, published studies focusing on MM generally included a limited patient number of less than 50 [7–9]. Under this circumstance, the retrospective study based on a public registry database is a good alternative. There were a few published papers focusing on high-grade meningioma by searching the Surveillance, Epidemiology, and End Results (SEER) database and National Cancer Database (NCDB) [10, 11]. However, most of them included a mixed patient cohort and did not take competing risk bias into consideration, which means the bias from the deaths caused by other diseases such as cardiovascular diseases rather than MM. A literature review of existing papers focusing on MM was presented in Supplementary Table 1.

577 adult patients with MM between 2004 and 2018 were included, and the specific records of patients' demographic, tumor characteristics, treatment methods, and cause of death in the SEER database were extracted for further analysis. This study aimed to explore the prognostic factors and figure out the optimal therapeutic strategies based on Fine-Gray competing risk regression model, which was performed with the adjustment of non-MM-caused mortality (non-MMCM) [12–15]. Moreover, a competing risk nomogram was conducted based on this relatively large-scale cohort in a long-time dimension, which could provide a more updated and deeper understanding of the prognosis and the treatment of MM patients.

2 Method

2.1 Participants

The most recent SEER release (November 2018) was obtained using the SEER* Stat 8.3.9.2 to identify adult patients with histologically proven intracranial MM between 2004 and 2018 (SEER operation code with specimen submitted to pathology, code 20, 21, 30, 40, and 50). ICD-O-3 codes 9530/3, 9531/3, 9532/3, 9533/3, 9534/3, 9535/3, 9537/3, 9538/3, and 9539/3 were defined as MM according to published research [16]. First, patients whose marital status and race as well as those whose tumor parameters (size, metastasis, and laterality) were unknown were excluded. In addition, a small number of patients who underwent radioactive implants, radioisotopes, and preoperative and intraoperative radiotherapy were excluded. Patients whose cancer-specific survival status was uncertain as well as those whose follow-up month status was unclear (due to incomplete dates and the possibility of no follow-up days) were excluded. 577 patients made up the final research population (Fig. 1).

2.2 Feature selection

The histology was divided into 9530/3 and others to ensure each subgroup contained sufficient cases for further analyses. The detailed histologic type was provided in Supplementary Table 2. The primary site of MM was classified as cerebral meninges and others for the same reason. The initial status of MM was defined by the "patient history" record. Patients with at least one prior record of WHO I or WHO II meningioma were defined as recurrent MM. The patients with age ≥ 65 years were defined as elderly patients. And considering the possible relationship between estrogen and

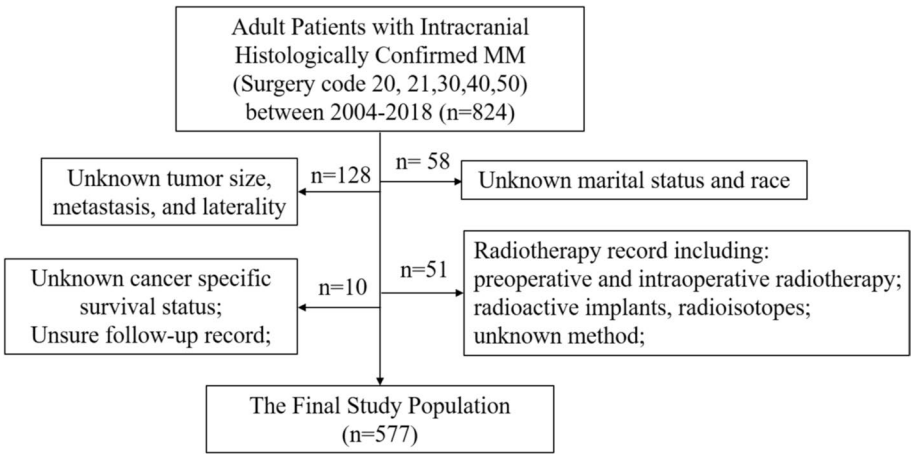


Fig. 1 Flowchart of patient's selection with MM selection. Surgery Code 0: no surgery of primary site; autopsy only; Code 10: no specimen sent to pathology; Code 22: resection of tumor of spinal cord or nerve; Code 90: surgery, no otherwise specified. *MM* malignant meningioma

meningioma, 45 years old was also selected as a cutoff [17, 18]. The best cut-off of tumor size (≤ 5.3 cm, and > 5.3 cm) was defined by x-tile software. The relationship between MM and other tumor was defined as no other tumor (one primary tumor only), before other tumor (first of 2 or more primary tumors), and after other tumor (second or third of the 2 or more primary tumors) based on the record of "sequence number" in SEER*Stat. Concerning the extent of surgery, we strictly used the original SEER record codes: 20 (local excision, biopsy), 21 (subtotal resection of tumor, STR of tumor), 30 (radical, total, gross resection of tumor, GTR of tumor), 40 (partial resection of lobe of brain), 55 (GTR of lobe of brain). The adjuvant therapy definition also strictly followed the original SEER records: PORT was characterized as beam radiation or none/unknown, and chemotherapy was recorded as yes or none/unknown.

2.3 Statistical analysis

By using the Chi-square test, the baseline patient characteristics of patients among age groups were compared. The change of surgical records and adjuvant therapy records over the year of diagnosis, the specific information of the patient initial status, and causes of non-MM-caused mortality were plotted by EXCEL. Two competing occurrences were identified as MM-caused mortality (MMCM) and non-MM-caused mortality (non-MMCM). Gray's test was used to assess the differences between subgroups after the Cumulative Incidence Function (CIF) curve was plotted by all covariates to demonstrate the probability of both MMCM and non-MMCM. Second, the link between the covariates for non-MMCM was shown using the univariate and multivariable Cox proportional regression models. Thirdly, prognostic variables for MMCM were found using univariate and multivariable Fine-Gray regression models. The proportionality hazard assumption was tested by a graphical method and was met (Supplementary Fig. 1). Finally, a corresponding nomogram was created to predict MMCM at 1-, 2-, and 5- years based on the discovered prognostic variables. By using the area under the receiver operating characteristic (ROC) curve (AUC) and the time-dependent ROC curve, the nomogram's discrimination performance was assessed. Additionally, a calibration curve was created using the bootstrap approach and 1000 resamples to gauge how well the predicted and actual survival probabilities tracked each other. R version 3.5.1 was used for all statistical analysis (http://www.r-project. org/). $P < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics of the study population

577 patients were included in the analysis. The median (min–max) age of diagnosis was 62 years old (18–100 years old) and the median overall survival time was 36 months (0–176 months). Generally, the cohort was slightly female-predominant (n = 301, 52.2%). We found the distribution of gender showed significant difference among age groups (P = 0.025): There were more female patients in the 18–44 year group (n = 44, 51.8%) and 45–64 year group (n = 142, 58.4%), while in the ≥ 65 year group, there were more male patients (n = 134, 53.8%). The median tumor size of the entire population was 47 mm (8–133 mm) and the proportion of patients with tumor size > 5.3 cm showed no significant difference among age groups (P = 0.101). Other demographic information (Race and marital status) and tumor characteristics (histology,

site, laterality, and metastasis) showed no significant difference among age groups (Table 1). Concerning the extent of surgery, the majority of patients were recorded as code 30 (n = 186, 32.2%) and code 55 (n = 135, 23.4%). The distribution of surgery codes showed no significant difference among age groups (P = 0.474) (Table 1), but presented a great difference among years of diagnosis (P < 0.001) (Supplement Fig. 2A). The results showed that the percentage of patients with surgery coded 40 and 55 dramatically decreased over the years while the percentage of patients coded 21 and 30 significantly increased after the year 2011. Regarding adjuvant therapy, 291 patients (50.4%) were treated with PORT and 36 patients (6.2%) were treated with chemotherapy, which showed no significant change over years. (Supplement Fig. 2B). The majority of patients (n = 520, 91.1%) had a de novo MM. And 57 patients (9.9%) had a recurrent MM, of which 33 patients had a history of benign meningioma and 24 patients had a history of atypical meningioma (Supplement Fig. 2C). Recurrent MM was significantly more common in ≥ 65 year group (n = 30, 12.0%) and 45–64 year group (n = 23.10.3%) compared with 18–44 year group (n = 2, 2.4%) (P = 0.034). 85 patients (14.7%) had other tumor(s) before MM and 52 patients (9%) had other tumor(s) after MM. There were more patients with other tumor(s) before MM in ≥ 65 year group (n = 50, 20.1%) while there were more patients with other tumor(s) after MM in 45-64y group (n = 26, 10.7%) (P = 0.019).

3.2 The interference of non-MMCM

At the time of data collected, 89 patients (15.4%) were dead of non-MM-specific causes. Heart disease (n = 13), lung and bronchus disease (n = 11), and cerebrovascular disease (n = 11) were the top three causes of non-MMCM (Supplement Figure 2D). The percentage of non-MMCM in 18–44 year, 45–64 year, and ≥ 65 year group were 4.7% (n = 4), 12.8% (n = 31), and 21.7% (n = 54) respectively (P < 0.001). The CIF curves showed that the incidence of non-MMCM was significantly higher in patients with older age (P < 0.001) and significantly lower in patients with no other tumor(s) (P < 0.001) (Supplement Fig. 3). Univariate Cox proportional hazard analysis showed that age group 45–64 year, age group ≥ 65 year, other tumor(s) before MM, and other tumor (s) after MM were significantly associated with non-MMCM (Supplementary Fig. 4). The multivariable Cox proportional hazard regression model also revealed that age group 45–64 year (HR 3.51, 95%CI 1.18–10.4, P = 0.02), age group ≥ 65 year (HR 9.11, %95CI 3.05–27.17, $P = 7.45 \times 10^{-5}$), other tumor(s) before MM (HR 4.99, 95%CI 2.88–8.66, $P = 1.05 \times 10^{-8}$), and other tumor(s) after MM (HR 2.94, 95%CI 1.67–5.17, $P = 1.8 \times 10^{-4}$) had an independently significant association with risk of non-MMCM (Fig. 2).

3.3 Prognostic factors and competing risk nomogram of MMCM

At the time of data collected, the percentage of MMCM was 31.7% (n = 183), which was 14.1% (n = 12), 25.9% (n = 63), and 43.4% (n = 108) in 18–44 year, 45–64 year, and ≥ 65 year group respectively (P < 0.001) (Table 1). The CIF curves revealed that patients in ≥ 65 year group had the highest incidence of MMCM (P < 0.001); Histologic type 9530/3 (P = 0.002), tumor size > 5.3 cm (P < 0.001), recurrent MM (P < 0.001), and receiving beam radiation (P = 0.034) presented a significantly higher incidence of MMCM (Supplement Figure 3). The Univariate Fine-Gray regression model showed that age group 45-64y (P = 0.003), age group ≥ 65y ($P = 6.2 \times 10^{-6}$), divorced (P = 0.007), widowed (P = 0.016), bilateral MM (P = 0.041), tumor size > 5.3 cm ($P = 5.1 \times 10^{-5}$), other histological types (P = 0.004), recurrent MM (P < 0.001), receiving beam radiation (P = 0.04), receiving chemotherapy (P = 0.002), and surgery code 40 (P = 0.02) were significantly associated with MMCM. The detailed HR and 95%CI were provided in Supplementary Figure 5. A multivariable Fine-Gray regression model was conducted to adjust the confounding effect of each variable. The results showed that age group ≥ 65 year (HR 3.55, 95%CI 1.88–6.69, $P = 9.3 \times 10^{-5}$), tumor size > 5.3 cm (HR 1.66, 95%CI 1.22–2.25, P = 0.001), recurrent MM (HR 4.26, 95%CI 2.97–6.11, $P = 3.8 \times 10^{-15}$), surgery code 21(HR1.66, 95%CI1.08–2.56, P = 0.02), surgery code 40 (HR 2.26, 95%CI 1.32–3.87, P = 0.003), and surgery code 55 (HR 1.69, 95%CI 1.12–2.51, P = 0.01) had an independently significant association with higher MMCM, while other histological types (HR 0.55, 95%CI 0.34–0.89, P = 0.02) had an independently significant association with lower MMCM (Fig. 3). Then, identified prognostic factors including age group, histology, surgery code, tumor size, and initial status were integrated to develop the prognostic competing risk nomogram (Fig. 4) to predict the 1-year, 2-year, and 5-year MMCM with AUC of 72.7 (66.7; 78.6), 78.7 (73.9; 83.6), and 79.6 (74.9; 84.2) respectively, which showed relatively good discrimination ability (Fig. 5A). Age group and initial status were the two strongest predictors. The time-depend AUC showed that the model represented good discrimination ability at different time points (Fig. 5B). Calibration plots showed good consistency between the nomogram-predicted probabilities and actual observations (Fig. 5C).

Table 1 Patient demographics, tumor characteristics and treatment options of 577 patients with histologically confirmed MM

characteristics	All	18–44 year	45–64 year	≥ 65 year	P-value
Population Size	577 (100)	85 (100)	243 (100)	249 (100)	
Sex					0.025†
Male	276 (47.8)	41 (48.2)	101 (41.6)	134 (53.8)	
Female	301 (52.2)	44 (51.8)	142 (58.4)	115 (46.2)	
Race					0.533
Other	69 (12.0)	7 (8.2)	30 (12.3)	32 (12.9)	
Black	89 (15.4)	12 (14.1)	43 (17.7)	34 (13.7)	
White	419 (72.6)	66 (77.6)	170 (70.0)	183 (73.5)	
Marital					< 0.001†
Single	115 (19.9)	38 (44.7)	53 (21.8)	24 (9.6)	
Divorced	58 (10.1)	5 (5.9)	29 (11.9)	24 (9.6)	
Married	343 (59.4)	42 (49.4)	149 (61.3)	152 (61.0)	
Widowed	61 (10.6)	0 (0.0)	12 (4.9)	49 (19.7)	
Size					0.101
≤ 5.3 cm	269 (64.0)	63 (74.1)	153 (63.0)	153 (61.4)	
> 5.3 cm	208 (36.0)	22 (25.9)	90 (37.0)	96 (38.6)	
Initial status					0.034
De novo	520 (91.1)	83 (97.6)	118 (89.7)	219 (88.0)	
Recurrence	57 (9.9)	2 (2.4)	25 (10.3)	30 (12.0)	
Histology					0.268
9530/3	470 (81.5)	64 (75.3)	199 (81.9)	207 (73.1)	
Other	107 (18.5)	21 (24.7)	44 (18.1)	42 (16.9)	
Site					0.346
Cerebral meninges	560 (97.1)	84 (98.8)	237 (97.5)	239 (96.0)	
Other	17 (2.9)	1 (1.2)	6 (2.5)	10 (4.0)	
Laterality					0.166
Unilateral	526 (91.2)	75 (88.2)	216 (88.9)	235 (94.4)	
Bilateral	15 (2.6)	2 (2.4)	9 (3.7)	4 (1.6)	
Midline	36 (6.2)	8 (9.4)	18 (7.4)	10 (4.0)	
Metastasis					0.11
No	559 (96.9)	85 (100)	232 (95.5)	242 (97.2)	
Yes	18 (3.1)	0 (0.0)	11 (4.5)	7 (2.8)	
Other tumor					0.019†
No	440 (76.3)	70 (82.4)	192 (79.0)	178 (71.5)	
Before MM	85 (14.7)	10 (11.8)	25 (10.3)	50 (20.1)	
After MM	52 (9.0)	5 (5.9)	26 (10.7)	21 (8.4)	
Surgery code					0.474
Code 30	186 (32.2)	24 (28.2)	79 (32.5)	83 (33.3)	
Code 20	91 (15.8)	9 (10.6)	37 (15.2)	45 (18.1)	
Code 21	115 (19.9)	23 (27.1)	51 (21.0)	41 (16.5)	
Code 40	50 (8.7)	8 (9.4)	18 (7.4)	24 (9.6)	
Code 55	135 (23.4)	21 (24.7)	58 (23.9)	56 (22.5)	
PORT					0.85
No/Unknown	286 (49.6)	50 (47.1)	123 (50.6)	123 (49.4)	
Beam Radiation	291 (50.4)	45 (52.9)	120 (49.4)	126 (50.6)	
Chemotherapy					0.122
No/Unknown	541 (93.8)	76 (89.4)	227 (93.4)	238 (95.6)	
Yes	36 (6.2)	9 (10.6)	16 (6.6)	11 (4.4)	
Competing risk survival					< 0.001†
Alive	305 (52.9)	69 (81.2)	149 (61.3)	87 (34.9)	
MMCM	183 (31.7)	12 (14.1)	63 (25.9)	108 (43.4)	
Non-MMCM	89 (15.4)	4 (4.7)	31 (12.8)	54 (21.7)	

Table 1 (continued)

[†]P < 0.05, statistically significant; Surgery Code 20: local excision, biopsy; Code 21: subtotal resection of tumor; Code 30: gross total resection of tumor; Code 40: Partial resection of lobe; Code 55: gross total resection of lobe

PORT post operative radiotherapy, *MMCM* malignant meningioma caused mortality

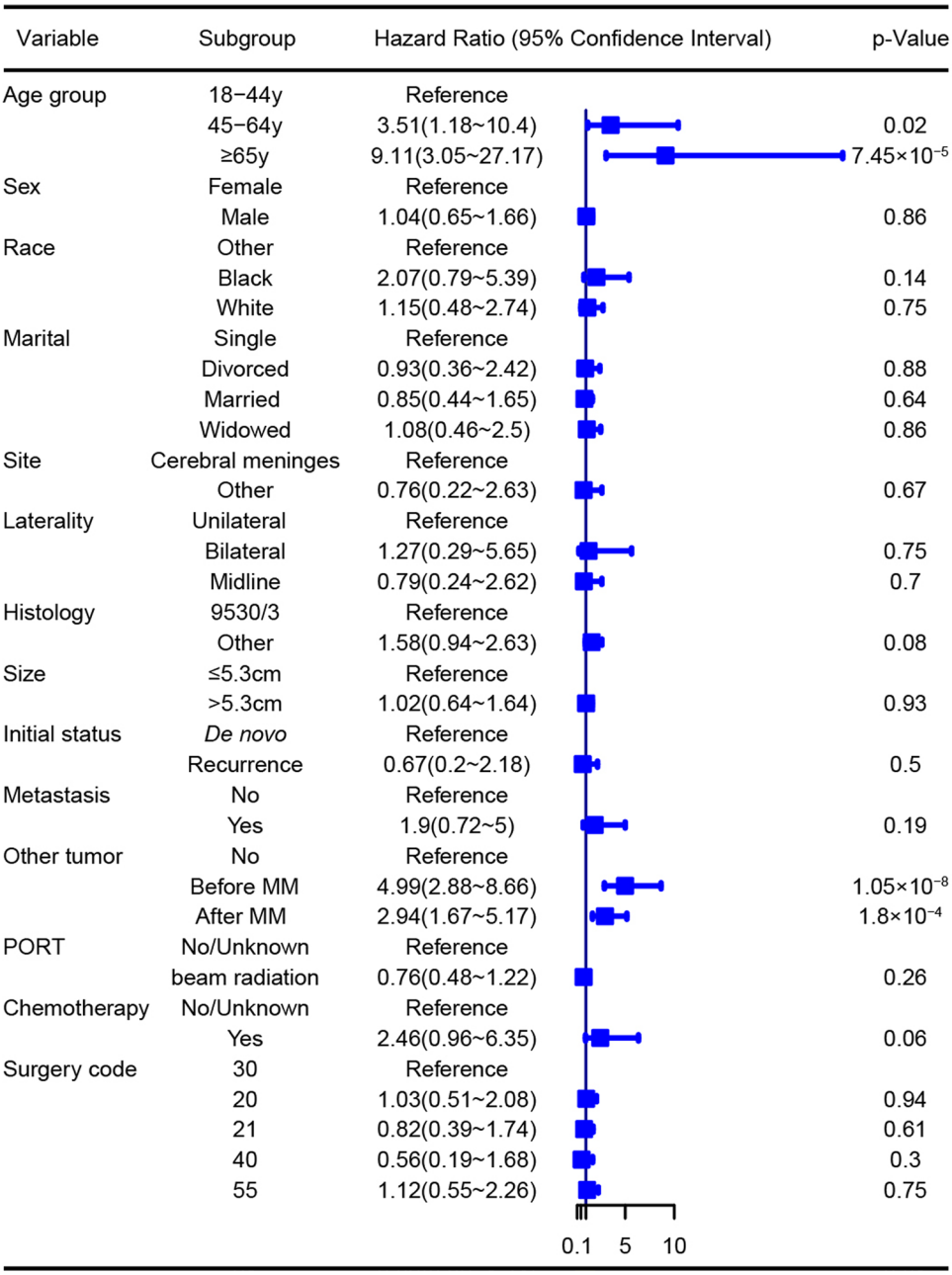


Fig. 2 Multivariate cox proportional hazard regression to identify prognostic factors for non-MMCM. P < 0.05, statistically significant; Surgery Code 20: local excision, biopsy; Code 21: subtotal resection of tumor; Code 30: gross total resection of tumor; Code 40: Partial resection of lobe; Code 55: gross total resection of lobe. *PORT* post operative radiotherapy, *MMCM* malignant meningioma caused mortality

4 Discussion

Malignant meningioma, also termed anaplastic meningioma, accounts for a small fraction of meningiomas, and its prognosis remains grim [19]. Given the low incidence of MM, there were not so many studies reporting the prognostic

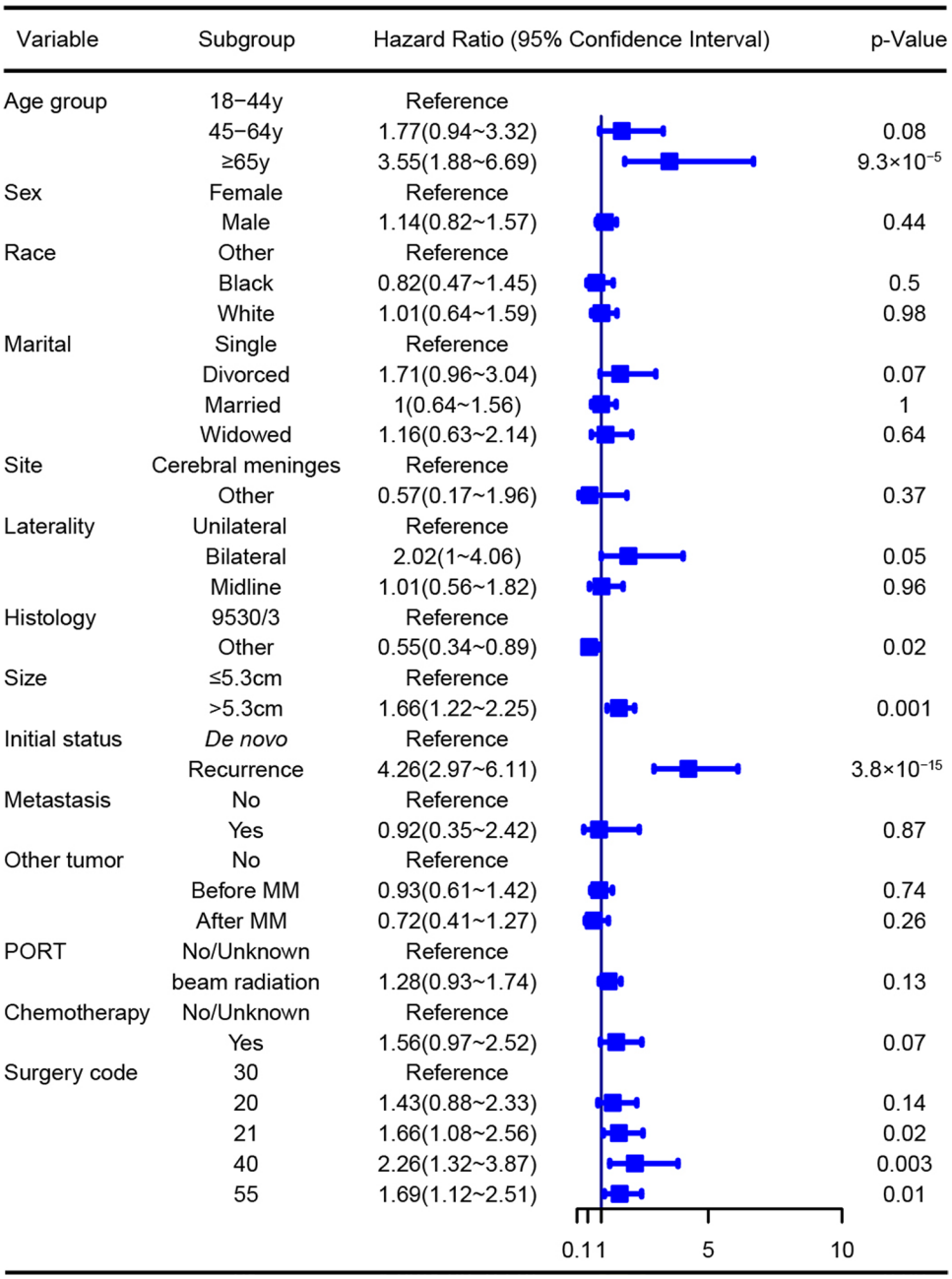
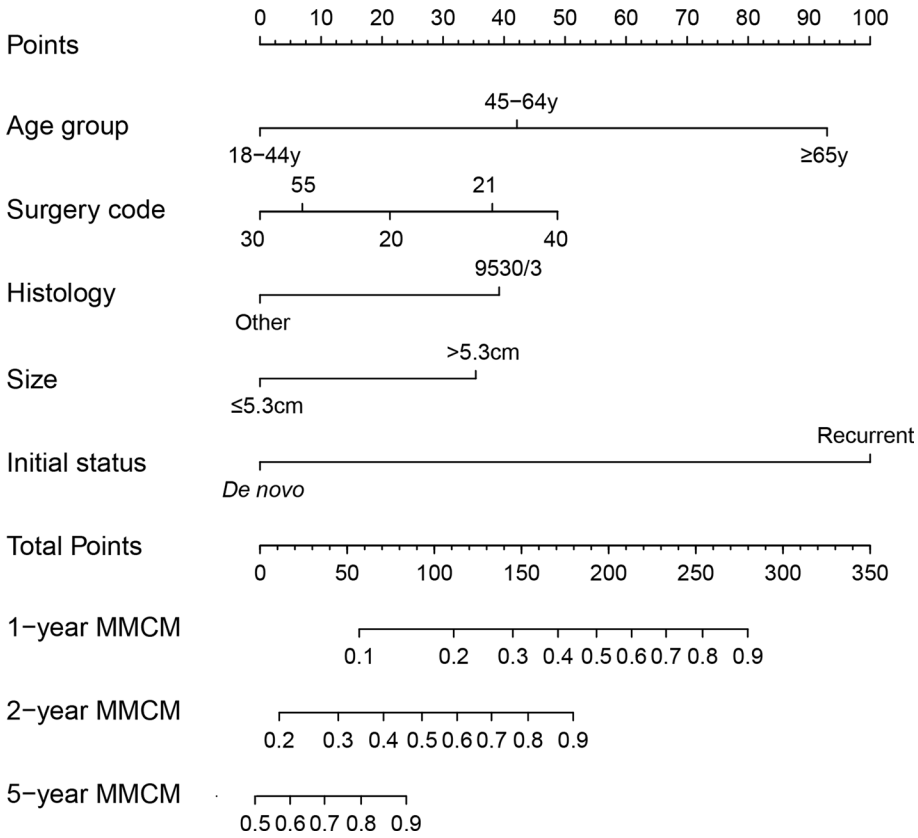


Fig. 3 Multivariable Fine-Gray regression to identify prognostic factors for MMCM. $P < 0.05$, statistically significant; Surgery Code 20: local excision, biopsy; Code 21: subtotal resection of tumor; Code 30: gross total resection of tumor; Code 40: Partial resection of lobe; Code 55: gross total resection of lobe. *PORT* post operative radiotherapy, *MMCM* malignant meningioma caused mortality

factors and treatment measures for MM patients. In this study, we developed a competing risk nomogram for MMCM based on the analyses of 577 histologically confirmed MM from 2004 to 2018 in the SEER database, which was not reported by published papers. Our results showed that the percentage of non-MMCM was 15.4% (n = 89) in the entire population and 21.7% (n = 54) in elderly patients. The CIF curves and Cox proportional hazard regression model also showed consistent results that age group and the existence of other tumor(s) were significantly related to non-MMCM. Under this circumstance, the conventional statistical methods including Kaplan–Meier curve and Cox proportional hazard model would cause non-negligible bias, and that's why Fine-Gray competing risk regression model was of great importance in this study [20]. This study tried to provide the most up-dated and deeper understanding of the prognosis and optimal treatment strategies based on the SEER database.

The median age of diagnosis of our cohort is 62 years old and 43.2% of patients (249/577) were elderly patients (≥ 65 year). Our result showed that older age was significantly associated with both non-MMCM and MMCM, which was



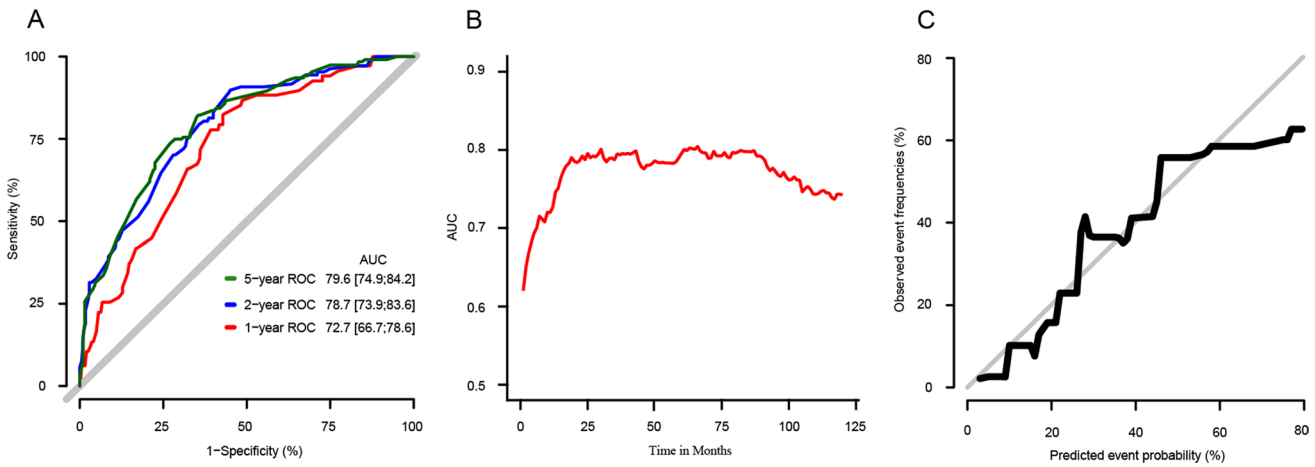


Fig. 5 **A** Areas under ROC curve of 1-, 2-, and 5-year MMCM and **B** Time-dependent ROC curve to reveal the discrimination of the model in different time points. **C**, Calibration curve to show the consistency between the nomogram predicted probabilities and actual observation. *ROC* receiver operating characteristic, *AUC* area under ROC

consistent with previous studies [5, 21–24]. In addition, the diagnostic age of patients with MM was reported to associate with tumor recurrence rate [23, 25]. Consistently, the percentage of recurrent MM in our cohort was 2.4%, 10.3%, and 12.0% in groups of 18–44 year, 44–64 year, and ≥ 65 year respectively. Our result showed sex was not significantly related to both non-MMCM and MMCM. Interestingly, we found that the distribution of sex showed a significant differences among different age groups: There were more female patients in 18–44 year group and 45-64 year group, while there were fewer female patients in ≥ 65 year group. We hypothesized that the incidence of meningioma decreased due to the significant decrease in sex hormone levels in women over 65 years old. It was reported that meningiomas were 2.8 times more frequent in females than in males, but the proportion of atypical and malignant meningiomas in males was twice as great as that in females [10]. There is evidence that the occurrence of meningiomas is closely related to sex hormones

[26]. Meningiomas rarely occur in prepubertal children whose circulating sex hormones are low, and there are studies indicating that meningiomas express progesterone and estrogen receptors [27, 28]. In addition, it has been reported that meningiomas grow rapidly during pregnancy and stop growing after delivery [29]. Yet more evidence is needed to support this view. Concerning tumor characteristics, our result showed that tumor size > 5.3 cm and histologic type 9530/3 were significantly associated with poor prognosis of patients with MM. Moreau JT reported that larger tumors were more malignant than smaller ones, and increased tumor size was associated with worse patient survival [10]. And larger tumor size is related to local tissue infiltration behavior, which may lead to a low success rate of complete tumor resection [30]. What's more, the function of "View patient histories" of SEER* Stat was made full use of to identify recurrent MM, which was not reported by published SEER-based studies about MM to the best of our knowledge. In our cohort, 57 (9.8%) patients were identified with recurrent MM, with a significant association with worse survival compared with de novo MM. Consistently, Peyre, M. reported that compared with de novo MM (n = 28), recurrent MM (N = 29) had a significant worse prognosis (P = 0.02) [31]. However, the patient history before 2004 was not provided in SEER*Stat, which will cause an underestimate of the percentage of recurrent MM. Despite the limitation, we tried our best to describe the cohort as accurately as possible.

Maximal safe resection is the most important treatment for malignant meningiomas [3, 32]. The purpose of microsurgery is to completely remove the tumor, including the involved dura and skull, which is equivalent to Simpson grade I resection[3]. We found intriguingly that the distribution of surgery patterns showed great difference with the change of treatment time. The results showed that the percentage of patients receiving operation coded as 40 (Partial resection of lobe of brain) and 55 (GTR of lobe of brain) were largely decreasing over time, while the percentage of which coded as 21 (STR of tumor) and 30 (GTR of tumor) significantly increased after the year 2011. This may be on account of the progress of microsurgical concepts and technology, which advocate the protection of normal brain structure and neurological function. The extent of resection has been reported to be a significant factor affecting both overall survival and progression-free survival [11, 33–35]. GJ Zhang et al. reported that GTR was a favorable factor for PFS and OS in a single institute-based retrospective study [36]. In another multi-center retrospective study, the authors reported that GTR was associated with better overall survival [34]. However, there were also studies suggesting that GTR was not correlated with better patient survival [22, 37]. Our results revealed that compared with patients accepting GTR of tumor, patients accepting STR of tumor, partial resection of lobe of brain and GTR of lobe of brain had a significantly worse MM-specific survival, suggesting the importance of resection degree to patient survival. Michael E Sughrue et al. reported their own experience that patients who received GTR possessed worse survival than patients who received near total resection (NTR) [33]. Our results also revealed that extended resection of brain lobe was associated with worse MM-specific survival of patients, suggesting that surgeons should also attempt to preserve normal brain tissue when pursuing gross resection of tumor. Radiotherapy has been implicated to be the commonly used therapy after surgery to control residual tumor [3, 38–40]. According to Orton A, PORT significantly increased the overall survival of patients with MM undergoing GTR and STR [11]. Another study suggested that patients with MM who received adjuvant radiotherapy had a longer survival time compared with those treated with surgery alone [37]. However, whether patients with MM can benefit from PORT still lacks powerful clinical trial results. Garzon-Muvdi T reported in another SEER based study that patients with atypical/malignant meningiomas who received radiotherapy had worse tumor related death compared with those who received surgery alone [5]. Nevertheless, the authors stated that this might be caused by the lack of specific radiation information acquired from SEER database and a patient selection bias. Meanwhile, Choi Y reported that patients with MM did not benefit from PORT and suggested that only patients diagnosed as atypical meningiomas without exclusive complete resection should be treated with PORT [35]. Another study based on the US National Cancer Database illustrated that adjuvant radiotherapy could not provide survival benefits for elderly patients (aged over 60) with MM after GTR [41]. Our results showed that the application of PORT did not exhibit a significant efficacy in patients with MM based on the multivariable Fine-Gray analysis. We believe that further large-scale clinical studies are needed to explore the benefits of PORT on the survival of MMP patients.

Though this study had strengths that benefited from the large patient cohort and the long MM-specific follow-up time, it still had innate limitations. Firstly, several important diagnostic and therapeutic information were not available from the SEER database, such as the detailed tumor histology, the venous sinus or skull invasion status, and the Simpson grades of resection, and the specific information of radiotherapy, which could affect the integrity and accuracy of the analysis. Secondly, there were modifications to WHO pathological diagnostic criteria in the past years, which may interfere with the accuracy of diagnosis and bring about patient selection bias. Thirdly, the molecular profiling of MM was not available from the database which might provide clinicians with a more comprehensive evaluation basis to guide

treatment strategies. Despite these limitations, we believe that the study deepens our understanding of this intractable disease and can help clinicians evaluate patient prognosis and formulate treatment strategies.

5 Conclusion

The competing causes of mortality should not be neglected in the management of MM. This study developed a competing risk nomogram including age group, tumor size, extent of resection, histology type, and initial status, which was discriminative and clinically useful. This study emphasized the importance of the GTR of tumor in the treatment of MM patients, which had a significantly lower incidence of MMCM compared with biopsy, STR of tumor, partial resection of lobe, and GTR of lobe. More studies were needed to evaluate the role of PORT in the treatment of MM.

Acknowledgements The authors acknowledge the efforts of the SEER Program cancer registries in creating the SEER database.

Author contributions ZL and XW designed the study and interpreted the data. HZ and JL did the statistical analysis and drafted the manuscript. XW and ZL revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding This work was supported by the Youth Natural Science Foundation of Changsha City (kq2202379) and Hunan Provincial Natural Science Foundation, China (No.2023JJ40830).

Data availability The data on which this article is based are available from the National Cancer Institute's Surveillance, Epidemiology, and End Results database at: https://seer.cancer.gov/, accessed on 21 February 2022.

Declarations

Competing interests The authors declare no competing interests.

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