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Patterns of care and survival of Chinese glioblastoma patients in the temozolomide era: a Hong Kong population-level analysis over a 14-year period

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Abstract

Background. The aim of this study is to address the paucity of epidemiological data regarding the characteristics, treatment patterns and survival outcomes of Chinese glioblastoma patients.

Methods. This was a population-level study of Hong Kong adult (>18 years) Chinese patients with newly diagnosed histologically confirmed glioblastoma between 2006 and 2019. The age standardized incidence rate (ASIR), patient-, tumor- treatment-related characteristics, overall survival (OS) as well as its predictors were determined.

Results. One thousand and ten patients with a median follow-up of 10.0 months were reviewed. The ASIR of glioblastoma was 1.0 per 100 000 population with no significant change during the study period. The mean age was 57 + 14 years. The median OS was 10.6 months (IQR: 5.2–18.4). Independent predictors for survival were: Karnofsky performance score >80 (adjusted OR: 0.8; 95% CI: 0.6–0.9), *IDH-1* mutant (aOR: 0.7; 95% CI: 0.5–0.9) or *MGMT* methylated (aOR: 0.7; 95% CI: 0.5–0.8) glioblastomas, gross total resection (aOR: 0.8; 95% CI: 0.5–0.8) and temozolomide chemoradiotherapy (aOR 0.4; 95% CI: 0.3–0.6). Despite the significant increased administration of temozolomide chemoradiotherapy from 39% (127/326) of patients in 2006–2010 to 63% (227/356) in 2015–2019 (*P*-value < .001), median OS did not improve (2006–2010: 10.3 months vs 2015–2019: 11.8 months) (OR: 1.1; 95% CI: 0.9–1.3).

Conclusions. The incidence of glioblastoma in the Chinese general population is low. We charted the development of neuro-oncological care of glioblastoma patients in Hong Kong during the temozolomide era. Although there was an increased adoption of temozolomide chemoradiotherapy, a corresponding improvement in survival was not observed.

Keywords

age standardized incidence rate | Chinese | glioblastoma | overall survival | temozolomide chemoradiotherapy

Glioblastoma is the commonest primary malignant brain tumor in adults accounting for 60% of gliomas and 15% of all central nervous system tumors.[1] In spite of standard-of-care treatment consisting of maximal safe resection followed by temozolomide (TMZ) chemotherapy and radiotherapy (RT), the prognosis remains poor.[2–4] Studies have documented the median overall survival (OS) of glioblastoma patients to vary from 12 to 15 months, but predominantly involved patients from Western countries.[1,5] In contrast, few epidemiologic studies of Chinese patients exist although distinct racial differences in the incidence, molecular profile and prognosis of Asians are increasingly being recognized.[6]

Brain tumor registries are vital in understanding the burden of disease and to harmonize care among patients from different regions or ethnicities.[7,8] In 2018, the National Brain Tumor Registry of China (NBTRC) was initiated to prospectively collect data from 2019 to 2024 from 54 participating hospitals.[8] However, until this registry is completed, there is a lack of patient-level clinical, tumor biomarker and treatment data among Chinese glioblastoma patients which are crucial for conducting multicenter clinical research. The Chinese Glioma Genome Atlas (CGGA), the only publicly-accessible database established in 2012, lacks information on patient Karnofsky performance status (KPS) and extent of resection, both known important predictors for OS.[9]

Hong Kong is a special administrative region in China with a population of 7.8 million where 94% of the population is ethnic Chinese.[10] Universal healthcare is delivered by the Hospital Authority (HA), a statutory body that manages all public hospitals, accounting for 90% of inpatient bed-days in the city. To address the lack of epidemiologic studies reviewing glioblastoma in adult Chinese patients, we established the Hong Kong Glioblastoma Registry, a population-level database to determine the incidence, treatment patterns, overall survival and its predictors over a 14-year period in the TMZ era. Comparisons were then made with publicly-accessible glioblastoma databases.

Materials and Methods

Study Population and Data Collection

This was a multicenter retrospective study that was approved by the HA institutional review board (reference number: KC/KE-18-0262/ER-4). Adult Chinese patients age 18 years or older with a new diagnosis of histologically confirmed cerebral glioblastoma from the 1 January 2006 to 31 December 2019 were reviewed. The pathological diagnosis was established in accordance with the prevailing World Health Organisation (WHO) Classification of Tumors of the Central Nervous System (CNS) at the time. During 2006, glioblastoma was diagnosed as specified by the 2nd edition of the WHO classification.[11] From 2007 to 2015, the diagnosis was made with regard to the 2007 3rd edition and from 2016 to 2019 in accordance with the 2016 4th edition.[12,13] Through the HA electronic medical record system, patients were first identified by the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) nomenclature for cancer topography, ie brain ("C711-C719"), and histological type, glioblastoma ("9440/3"). Patients with the histological codes for gliosarcoma/gliofibroma ("9442") or giant cell glioblastoma ("9441") were excluded as they represent prognostically and epidemiologically distinct groups. Clinical data was broadly categorized into patient-, tumor- and treatment-related factors. Patient-related data included age, gender and pretreatment KPS. Tumor-related data included its location, isocitrate dehydrodegenase-1 (*IDH-1*) mutation status and promoter O^6-methylguanine-methyltransferase (p*MGMT*) methylation status. The former was determined by immunohistochemistry or by DNA sequencing when the results were equivocal or if the patient was younger than 55 years-old. p*MGMT* methylation analysis was performed by methylation-specific polymerase chain reaction. Extent of resection (EOR) was defined according to the neurosurgeon's description from operation records and was categorized into either biopsy, subtotal resection (STR) or gross total resection (GTR).

The primary endpoint was OS, defined as the date of the first surgery that confirmed the diagnosis of glioblastoma until death. Cases were subdivided into 3 time periods according to the year of diagnosis. The period between 1 January 2006 and 31 December 2010, was considered the "incipient" phase when TMZ + RT and the importance of p*MGMT* methylation testing was increasingly recognized.[2,14] In Hong Kong, temozolomide was first incorporated into the Hospital Authority's drug formulary in 2010, but was listed as a self-financed item. Between 1 January 2011 and 31 December 2014 was considered the "transition" phase, when conditional governmental safety net funding for TMZ to treat p*MGMT* methylated glioblastoma patients was approved and a renewed appreciation for significance of EOR on prognosis was established.[15] From 1 January 2015 to 31 December 2019 was determined the "modern" era where standardized biomarker testing according to the 4th WHO Classification was made widely available and safety net governmental funding was expanded to all glioblastoma patients regardless of p*MGMT* methylation status.[12] Cases were censored by 31 October 2021.

Database Comparisons

Three publicly accessible clinical databases of glioblastoma patients were interrogated. They were: The Cancer Genome Atlas (TCGA, https://cancergenome.nih.gov) using the glioblastoma dataset made available in 2013; the Chinese Glioma Genome Atlas (CGGA,

http://cgga.org.cn, dataset: mRNAseq_693) made available in 2015 and the REpository for Molecular BRAin Neoplasia DaTa (REMBRANDT) 2018 database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE108474, dataset: GSE108474).[9,16,17] The CGGA is a database consisting of clinically-annotated glioblastoma patient-derived molecular data collected from a consortium of six academic institutions from Northern China.[9] The REMBRANDT project was a joint initiative of the US National Cancer Institute and the National Institutes of Neurological Disorders and Stroke that consisted of prospectively collected clinical-molecular data acquired from 14 academic institutions in North America from 2004 to 2006.[17] Only adult patients with new histologically confirmed glioblastoma were included in this study (Figure 1). The characteristics and OS outcomes of patients from these databases were then compared to the Hong Kong cohort.

Statistical Analysis

Age-standardized glioblastoma incidence per 100 000 Hong Kong inhabitants was calculated using standard population data from the Hong Kong Annual Digest of Statistics, Census and Statistics Department, The Government of the Hong Kong Special Administrative Region.[18] The relative annual change in the age-standardized incidence rate (ASIR) was estimated using Poisson regression and the Davies' test was utilized to detect significant changes in incidence trends. Survival analysis was performed using multivariate Cox proportional hazards modeling. Survival probabilities were represented by Kaplan-Meier plots and subgroup analysis by log-rank testing. Independent samples *t*-testing and chi-squared testing was conducted to compare variables across databases. One-way analysis of variance (ANOVA) was also carried out for continuous data across different categorical variables. A *P*-value of <.05 was considered statistically significant. Competing risk analysis was not performed since glioblastoma patients generally had short survival durations. All tests were performed utilizing the Statistical Package for the Social Sciences software version 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 1059 consecutive Hong Kong patients were identified with newly diagnosed histologically confirmed glioblastoma during this 14-year period. One thousand and ten patients were reviewed for this study. Forty-nine were excluded since 23 (2.2%) were younger than 18 years old and 26 (2.5%) were not Chinese. The demographics, tumor and treatment data of these patients are presented in Table 1.

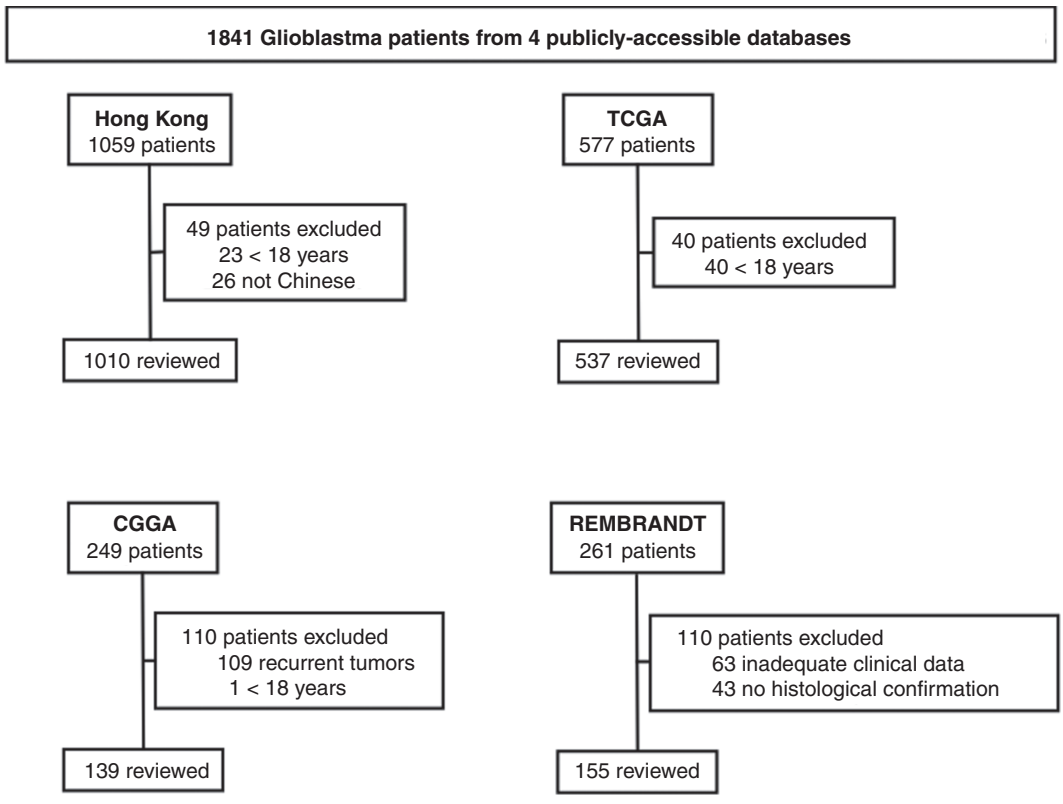

Figure 1. Flow diagram illustrating the total number of adult glioblastoma patients reviewed from each database. N.B. TCGA, The Cancer Genome Atlas; CGGA, Chinese Glioma Genome Atlas; REMBRANDT, Repository of Molecular Brain Neoplasia Data.

Table 1. Patient, Tumor and Treatment Characteristics for Each Glioblastoma Treatment Phase

	Total	Incipient phase 2006–2010	Transitional phase 2011–2014	Modern phase 2015–2019
	***n* = 1010 (%)**	***n* = 326 (%)**	***n* = 328 (%)**	***n* = 356 (%)**
Patient factors				
Age at diagnosis, years, mean ± SD	57.0 ± 13.6	57.0 ± 14.4	59.0 ± 13.6	60.0 ± 12.7
Age categories				
18–49	260 (26)	96 (30)	86 (26)	78 (22)
50–59	275 (27)	86 (27)	88 (27)	99 (28)
60–69	286 (28)	72 (22)	100 (31)	116 (33)
70–79	163 (16)	57 (18)	47 (14)	59 (17)
≥80	26 (3)	15 (5)	7 (2)	4 (1)
Male	626 (62)	204 (63)	206 (63)	215 (60)
KPS				
<80	594 (59)	169 (52)	215 (66)	209 (59)
≥80	416 (41)	157 (48)	113 (35)	147 (41)
Follow-up time, months, median (IQR)	10 (5–20)	10 (5–20)	10 (4–18)	11 (5–21)
Tumor factors				
Location by lobe				
Frontal	379 (37)	124 (38)	102 (31)	133 (37)
Temporal	270 (27)	86 (27)	94 (29)	91 (26)
Parietal	229 (23)	65 (20)	81 (25)	82 (23)
Central core*	56 (6)	14 (3)	18 (6)	21 (6)
Occipital	41 (4)	13 (4)	12 (4)	16 (5)
Cerebellum	31 (3)	12 (4)	13 (4)	6 (2)
Brainstem	4 (0.4)	0	2 (0.6)	2 (0.6)
IDH-1 status[†] (valid %)				
Mutant	51 (12)	5 (56)	14 (15)	33 (11)
Wild-type	362 (88)	4 (44)	82 (85)	276 (89)
Missing	597	317	232	47
p*MGMT* status[‡] (valid %)				
Methylated	303 (45)	56 (44)	121 (46)	127 (44)
Unmethylated	375 (55)	70 (56)	140 (54)	165 (57)
Missing	332	200	67	64
Treatment factors				
Extent of resection				
GTR	312 (31)	100 (30)	103 (31)	110 (31)
STR	545 (54)	184 (57)	173 (53)	187 (53)
Biopsy	153 (15)	42 (13)	52 (16)	59 (17)
TMZ + RT	516 (51)	127 (39)	161 (49)	227 (63)
Chemotherapy only	67 (7)	25 (8)	17 (5)	25 (7)
RT only	273 (27)	107 (33)	100 (30)	66 (19)
No adjuvant treatment	155 (15)	67 (21)	50 (15)	38 (11)

N.B. KPS, Karnofsky performance status; *IDH-1*, isocitrate dehydrogenase-1; p*MGMT*, methylguanine-methyltransferase promoter; GTR, gross total resection; STR, subtotal resection; TMZ, temozolomide; RT, radiotherapy.
*Central core comprises of the insula, basal ganglia and the thalamus.
[†]41% (413/1010) specimens had *IDH-1* mutation testing.
[‡]67% (678/1010) specimens underwent p*MGMT* methylation testing.

Follow-up was complete for 98% (990/1010) of patients. The mean follow-up duration was 16.6 + 19.3 months (median follow-up: 10.0 months; IQR: 5.0–19.8). The ASIR of glioblastoma was 1.0 per 100 000 population and there was no significant year-on-year difference (*P*-value: .66). The mean age of patients was 57.0 + 13.6 years with a median of 59.0 years (IQR: 49.0–66.0). The peak incidence was at the 50-to-69 years age group (Figure 2). The majority were men with a female: male ratio of 1: 1.6 and 41% (416/1010) of patients had a preoperative KPS of 80–100. For those with the relevant tumor molecular biomarker testing performed, 45% (303/678) of glioblastomas were p*MGMT* methylated and 12%, (51/413) were *IDH-1* mutant.

Patterns of Care in Hong Kong

Only 31% (312/1010) of patients underwent gross total tumor resection. The majority had subtotal resections (535, 54%) and 15% (152/1010) had tumor biopsies (Table 1). Half of patients (516, 51%) received adjuvant TMZ + RT and 27% (273) had RT alone. For the time periods of care in the TMZ era, 326 (32%) patients were diagnosed in the incipient phase (2006–2010), 328 (32%) patients in the transitional phase (2011–2014) and 356 (35%) patients in the modern phase (2015–2019). The proportion of tumors that were grossly resected were comparable over the 3 time-periods (*P*-value: .42). In contrast, there was a significant stepwise increase in the number of patients that received TMZ + RT from the initial incipient phase: 39% (127), to the transitional phase: 49% (161) and the modern phase: 63% (227) (*P*-value < .001). Consequently, significantly fewer patients received conservative management reflecting a trend for adopting standard-of-care therapy (*P*-value < .001). Similarly, p*MGMT* and *IDH-1* molecular tumor profiling was more increasingly performed. In the transitional phase, there was a considerable increase in p*MGMT* methylation testing (80%, 261/328) compared to the previous incipient phase (39%, 126/326) that coincided with the rise in TMZ + RT (*P*-value: .03). *IDH-1* mutation testing has also increased from just 3% (9/326) in the incipient phase to 87% (309/356) in the modern phase (*P*-value: .04). The independent factors that influenced the prescription of TMZ + RT for Hong Kong patients were: age > 70 years (adjusted OR: 0.7; 95% CI: 0.5–0.9), a preoperative KPS > 80 (aOR: 2.0; 95% CI: 1.5–2.9), methylated tumors (aOR: 1.6; 95% CI: 1.1–2.1) and GTR (aOR: 1.4; 95% CI: 1.0–2.0).

Trends and Predictors of Overall Survival

The median OS (mOS) for Chinese glioblastoma patients was 10.6 months (IQR: 5.2–18.4) with the proportions of patients achieving 12- and 24-month survival being 45% (464/1010) and 20% (204/1010), respectively. From univariate analysis, predictors for improved OS were patient age < 70 years (log-rank test, *P*-value: .04), a preoperative KPS of > 80 (*P*-value < .001), *IDH-1* mutant status,

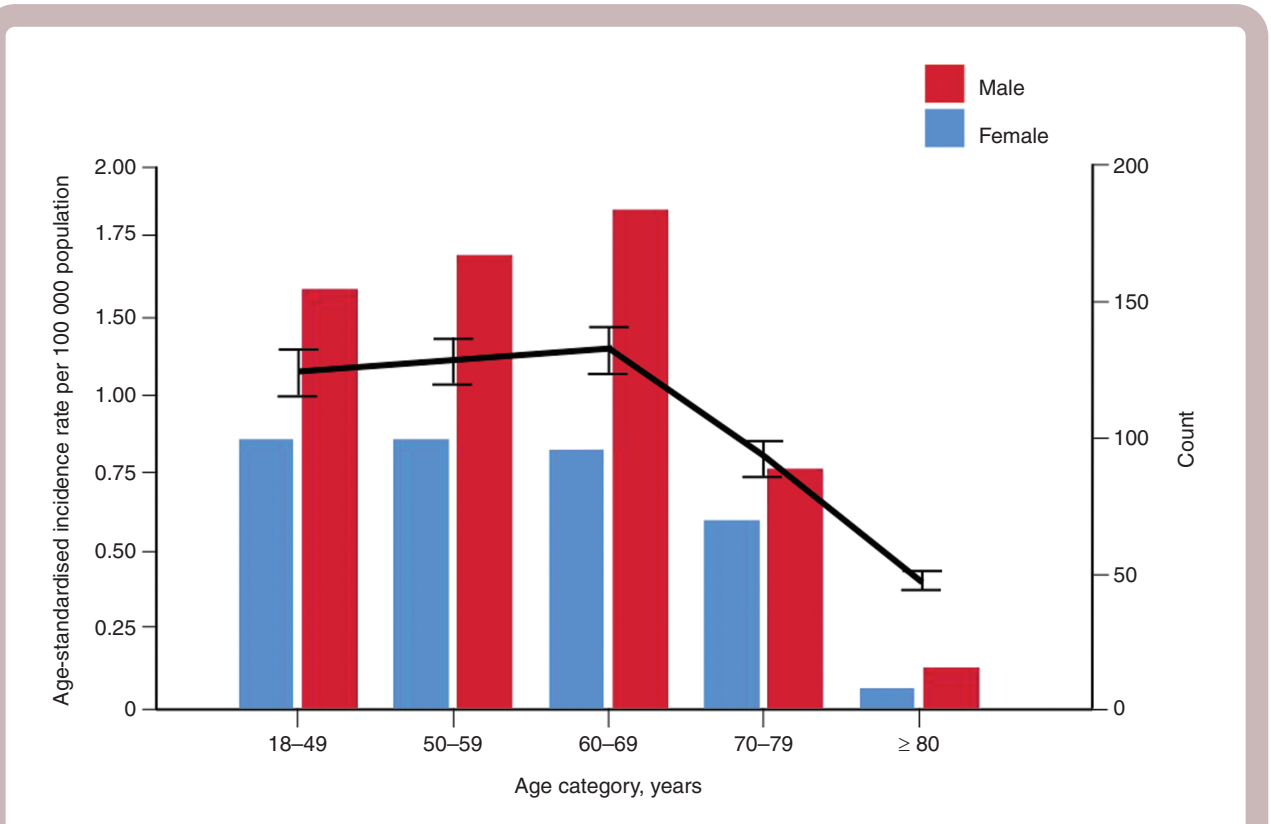

Figure 2. Age distribution of patients from the Hong Kong Glioblastoma Registry. Graph depicting the age-standardized incidence rate per 100 000 population for each age group (black line; left *y*-axis) and the absolute number of patients per group dichotomized by gender (right *y*-axis).

(*P*-value < .001), p*MGMT* methylated status (*P*-value < .001), GTR (*P*-value: .03) and TMZ + RT (*P*-value < .001) (Figure 3). Multivariate analysis revealed that patients with a KPS of > 80 (adjusted OR: 0.8; 95% CI: 0.6–0.9), *IDH-1* mutant (aOR: 0.7; 95% CI: 0.5–0.9) or p*MGMT* methylated (aOR: 0.7; 95% CI: 0.5–0.8) glioblastomas, GTR (aOR: 0.8; 95% CI: 0.5–0.8) and TMZ + RT (aOR 0.4; 95% CI: 0.3–0.6) were independent predictors for OS (Table 2). Since glioblastoma p*MGMT* status was identified as a major determinant for prescribing standard-of-care treatment, a subgroup analysis was performed to evaluate the efficacy of TMZ + RT vs adjuvant RT alone for patients with p*MGMT* unmethylated tumors (Supplementary Table 3). 56% (211/375) of these patients received TMZ + RT and a survival benefit was observed compared to those that only had RT. The mOS of patients was 13.6 months (IQR: 9.1–20.4) compared to 9.8 months (IQR: 6.8–15.3) for those that received RT alone (*P*-value: .004). After adjusting for age, preoperative KPS, extent of resection and *IDH-1* mutation status, TMZ + RT was an independent significant determinant of OS with an aOR of 1.6 (95% CI: 1.0–2.3) (Figure 4a).

Although an increase in OS was observed over the 14-year time period, the rise was insignificant (*P*-value: .41). For the incipient phase the mOS was 10.3 months (IQR: 5.6–20.4), the transition phase, 10.8 months (IQR: 4.6–18.7) and the modern phase was 11.9 months (IQR: 5.3–22.0) (Figure 4b). The 12-, 24-, 36-month survival rates for each phase were also comparable (Supplementary Table 4). Survival outcomes also did not improve with time when subgroup analyses were performed for patients younger than 60 (*P*-value: .56) or 70 years (*P*-value: .75).

Comparison with Publicly Accessible Glioblastoma Databases

A total of 1841 adult glioblastoma patients from four independent cohorts, including the present registry, were analyzed. The Hong Kong registry comprised 55% (1010/1841) of patients (Supplementary Table 5). The age (*P*-value: .44) and gender distribution (*P*-value: .10) of Hong Kong patients were similar to the other databases. A significantly larger proportion of TCGA cohort patients had a preoperative KPS > 80 (56%) compared to the Hong Kong and REMBRANDT cohort patients where only 40% had good functional performance (*P*-value < .001). However, a greater proportion of tumors were *IDH-1* mutant in both the Hong Kong (12%) and CGGA cohorts (18%) compared to TCGA cohort (7%) (*P*-value < .01). With regard to treatment, 31% of Hong Kong patients underwent GTR which was comparable to the REMBRANDT cohort (35%) (*P*-value: .09). No such data was available from the TCGA and CCGA databases. Only half of Hong Kong patients (51%) received TMZ + RT which was similar to the TCGA (41%) and REMBRANDT (44%) cohorts, but was significantly lower than the CGGA cohort (73%) (*P*-value < .001).

The mOS of Hong Kong registry patients was the shortest of the publicly-accessible databases, but was insignificant compared to patients of the TCGA (*P*-value: .11) and CGGA (*P*-value: .09) cohorts (Tables 2, Supplementary Table 5 and Figure 5). A significantly larger proportion of CGGA cohort patients were able to achieve 12- and 24-month survival compared to the Hong Kong and TCGA cohorts (*P*-value: < .01). Patients of the REMBRANDT cohort had a substantially longer mOS as well as the highest 12-, 24-, 36-month and 5-year survival rates among all the databases (*P*-value < .001) (Supplementary Table 5).

Discussion

The age-standardized incidence rate of glioblastoma among Chinese is 1.0 per 100 000 person-years and has remained unchanged during this 14-year study period. Previously cited rates for Chinese of 1–4 per 100 000 were founded on individual institutional brain tumor registries with limited information regarding a definitive histological diagnosis of glioblastoma and follow-up rates.[19,20] In comparison, the current registry reviewed population-based public healthcare provider data with a 98% follow-up rate. The incidence of glioblastoma among Chinese is lower than Caucasians from North America (3.9 per 100 000 person-years) or those from European countries such as Switzerland (3.9 per 100 000), Austria (3.4 per 100 000), France (3.3 per 100 000), Finland (2.9 per 100 000) and Denmark (males: 6.3 per 100 000; females: 3.9 per 100 000).[6,21–25] Chinese glioblastoma incidence was also lower than the Japanese (2.6 per 100 000), Indians (2.5 per 100 000), African-Americans (1.8 per 100 000) and Asian Pacific Islanders (1.5 per 100 000), but similar to South Koreans (1.1 per 100 000).[6,26–28] Previous investigators commented that the ASIRs of glioblastoma were higher for industrialized nations, attributing the cause to socio-economic differences or under reporting among low-and-middle-income countries. Yet developed Asian countries such as Japan and South Korea have consistently recorded a lower incidence than Caucasians.[29] In Hong Kong, an affluent South-east Asian city that offers universal healthcare, our findings support the possibility of an underlying racial predisposition to gliomagenesis that is seldom explored. Some have demonstrated that among non-Caucasian astrocytoma patients a significantly higher proportion of tumors had *TP53* mutations compared to Caucasians.[30,31] But these studies reviewed a limited number of patients and other epidemiological surveys have so far failed to detect a distinct molecular profile among Asians.[32]

The most significant therapeutic breakthrough for glioblastoma in the last 15 years was the introduction of TMZ + RT as standard-of-care treatment.[2,5] The landmark trial that compared multimodal therapy to RT alone documented an improvement in mOS from 12.1 to 14.6 months.[2] Multimodal therapy has subsequently been incorporated in several clinical practice guidelines as level I recommended first-line treatment.[3,4] A meta-analysis revealed a doubling of 2-year survival rates since its adoption from 9% to 18%.[5] The current study determined the territory-wide mOS of Chinese patients in the TMZ-era was 10.6 months which is in line with other population-level studies from western Europe, North America and Australia where mOS ranged from 9.7 to 11.7 months.[23–25,33,34] The 2-year survival rate of 20.0% was also comparable to other national brain tumor registry data recording rates of 16.6 to 25.0%.[23–25,33,34] It is a common to observe

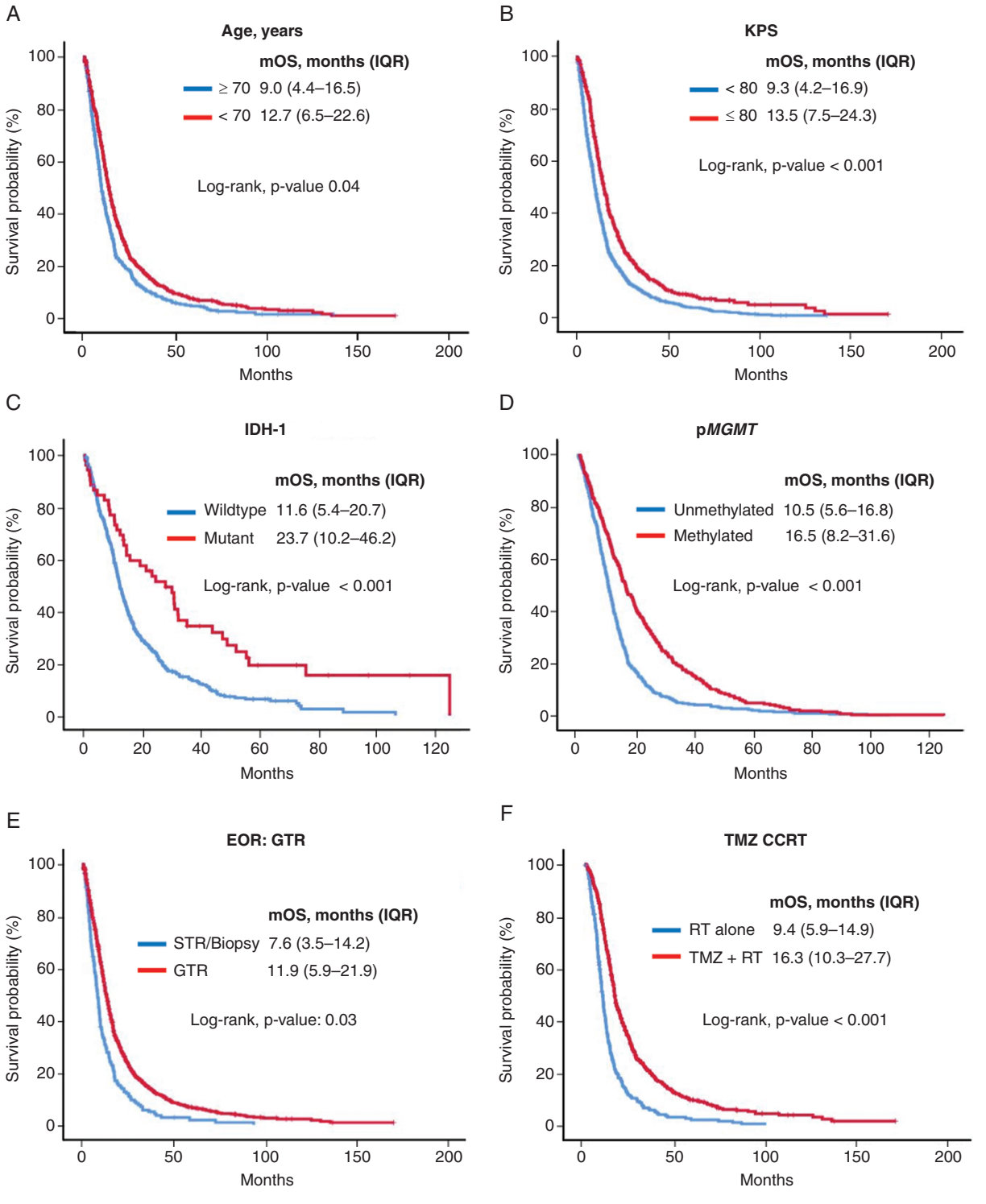

Figure 3. Kaplan-Meier overall survival analysis of identified patient-, tumor- and treatment-related prognostic factors for Hong Kong adult glioblastoma patients. Age < 70 years (a), a preoperative Karnofsky performance score (KPS) of > 80 (b), *IDH-1* mutant tumors (c), p*MGMT* methylated tumors (d), gross total resection (GTR) (e) and administration of TMZ + RT (f) conferred a survival benefit. N.B. extent of resection (EOR).

shorter OS durations in real-world cancer studies compared to that reported in clinical trials. Rigorous subject eligibility criteria including age, functional performance, comorbidities, study protocol-driven scanning schedules for early detection of tumor recurrence, as well as enhanced access to care are frequent sources of selection

Table 2. Predictors for Overall Survival and Comparison with Publicly Accessible Databases

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Patient factors						
Age at diagnosis, years						
<70	1 (Ref)	–	–	1 (Ref)	–	–
≥70	13.4	12.3–14.4	0.04	1.1	0.9–1.4	NS
Gender						
Female	1 (Ref)	–	–	1 (Ref)	–	–
Male	1.1	1.0–1.3	NS	1.2	0.6–1.0	NS
KPS						
<80	1 (Ref)	–	–	1 (Ref)	–	–
≥80	0.7	0.6–0.8	<0.001	0.8	0.6–0.9	0.02
Tumor factors						
IDH-1 status						
Wildtype	1 (Ref)	–	–	1 (Ref)	–	–
Mutant	0.5	0.4–0.7	<0.001	0.7	0.5–0.9	0.04
p*MGMT* status						
Unmethylated	1 (Ref)	–	–	1 (Ref)	–	–
Methylated	0.6	0.5–0.7	<0.001	0.7	0.5–0.8	<0.001
Treatment factors						
EOR						
Biopsy or STR	1 (Ref)	–	–	1 (Ref)	–	–
GTR	0.8	0.8–1.0	0.03	0.8	0.6–1.0	0.05
Adjuvant treatment						
No TMZ + RT	1 (Ref)	–	–	1 (Ref)	–	–
TMZ + RT	0.4	0.3–0.5	<0.001	0.4	0.3–0.6	<0.001
Treatment era						
Incipient 2006–2010	1 (Ref)		–	1 (Ref)	–	–
Transitional 2011–2014	0.9	0.7–1.1	NS	0.9	0.7–1.3	NS
Modern 2015–2019	0.9	0.7–1.0	NS	0.9	0.7–1.2	NS
Glioblastoma database						
Overall survival						
Hong Kong	1 (Ref)	–	–	1 (Ref)	–	–
TCGA	0.90	0.81–1.00	NS	0.96	0.85–1.08	NS
CGGA	0.97	0.80–1.17	NS	0.86	0.70–1.04	NS
REMBRANDT	0.67	0.56–0.79	<0.001	0.60	0.50–0.71	<0.001

N.B. Ref, reference; TCGA, The Cancer Genome Atlas; CGGA, Chinese Glioma Genome Atlas; REMBRANDT, Repository of Molecular Brain Neoplasia Data; KPS, Karnofsky performance status; *IDH-1*, isocitrate dehydrogenase-1; p*MGMT*, methylguanine-methyltransferase promoter; GTR, gross total resection; STR, subtotal resection; TMZ, temozolomide; RT, radiotherapy; NS, not significant.

bias.[35] To illustrate, REMBRANDT cohort patients survived longer compared to Hong Kong cohort patients despite having similar GTR and TMZ + RT rates. It is postulated that since REMBRANDT patients were treated at major US academic cancer centers there they likely represented a highly selected cohort.[17] A review of glioblastoma registry patients for potential phase III trial eligibility noted that 59% would not fulfill recruitment criteria emphasizing the lack of real-world representation in the literature.[35]

Our study validated established prognostic factors for survival among Chinese glioblastoma patients.[2–4,14,15,36] Patients had a better prognosis if they had good preoperative functional performance, had tumors that were either *IDH-1* mutated or p*MGMT* methylated, that underwent gross total resection or received TMZ + RT. The significance of extent of resection and functional performance reflects the importance of maximal safe resection, the only modifiable prognosticator for survival

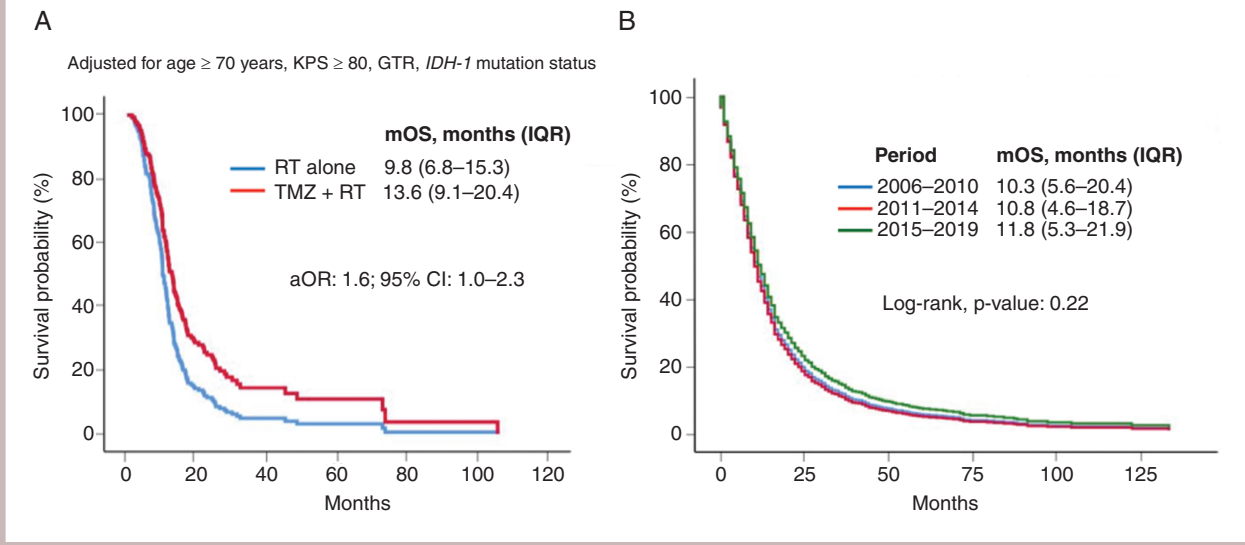

Figure 4. Subgroup Kaplan-Meier curve survival analysis of p*MGMT* unmethylated glioblastoma patients (a). Those that received TMZ + RT had significantly longer median overall survival than patients that had RT alone after adjusting for confounding factors. No significant improvement in median overall survival of adult glioblastoma patients was observed throughout the three phases of Hong Kong neuro-oncological care (b). N.B. incipient phase: 2006–2010, transitional phase: 2011–2014 and the modern phase: 2015–2019.

regardless of molecular subtype.[15,36] GTR was achieved in 31% of Hong Kong patients which was similar to the REMBRANDT cohort (35%) (Supplementary Table 5). In comparison, a systematic analysis of 37 studies revealed that the mean rate of GTR was 41% and concluded that patients were 61% more likely to achieve 1-year survival than those that received STR.[36] A single-institution study of 967 Chinese patients documented a demonstrable improvement in mOS from 16.3 months to 18.2 months by adopting intraoperative MRI (iMRI) and brain mapping techniques to achieve a GTR rate of 63%.[37] iMRI, 5-aminolevulinic acid (5-ALA) fluorescence-guided resection and brain mapping are surgical techniques that have consistently been proven to increase EOR translating to improved OS.[38–40] In Hong Kong iMRI facilities are not available and fewer than 10% of patients underwent fluorescence-guided resection or awake craniotomy for tumor resection. Another contributing factor for the lower GTR rate could be due to the high proportion of patients that had poor preoperative KPS upon presentation (59%). Concerns for inducing further neurological injury may have interfered with attempts for aggressive resection, especially when functional performance was identified as a major determinant for prescribing subsequent TMZ + RT in our locality.

This study also revealed a trend for longer survival among glioblastoma patients treated in mainland Chinese institutions (CGGA) than in Hong Kong. Apart from the significantly higher number of mainland Chinese patients having good preoperative KPS than in Hong Kong (56% vs 41%; *P*-value < .001) another factor accounting for this discrepancy was the notable difference in prescribing TMZ + RT among CGGA patients (74% vs 51%; *P*-value < .001) (Supplementary Table 5).[9,37] In Hong Kong, p*MGMT* unmethylated glioblastoma patients were less likely to receive standard-of-care treatment.

There is ample evidence establishing p*MGMT* methylation as an important prognostic and predictive biomarker.[14] From our subgroup analysis of unmethylated tumor patients, we noted that TMZ + RT continued to confer a survival benefit compared to RT alone (13.6 months vs 9.8 months). Whether TMZ should be withheld from these patients is a subject of debate.[41,42] Two prospective trials of elderly glioblastoma patients, defined as either >65 years or >60 years, compared upfront TMZ alone vs RT alone and concluded that chemotherapy for this relatively frail population was detrimental for those with unmethylated tumors.[43,44] In addition, several phase III randomized-controlled trials (RCT) that compared TMZ + RT with novel agents did not detect shorter OS among unmethylated tumor patients when TMZ was omitted. Nevertheless, the majority of these patients continue to be treated with TMZ in the United States, Europe and China.[23,37,45] In Hong Kong, this practice is also increasingly being observed (Table 1). Apart from the difficulty of withholding a well-tolerated chemotherapeutic agent for those with the poorest prognosis, there are a number of reasons for prescribing TMZ regardless of p*MGMT* methylation status. First, there is insufficient evidence to withhold TMZ from patients <65 years of age.[41] Second, there is the marginal, but clinically meaningful survival advantage observed in a proportion of unmethylated tumor trial subjects ranging from 4 to 6 weeks.[46] Third, a recent meta-analysis of 5 clinical trials that reviewed 655 unmethylated glioblastoma patients, failed to draw definitive conclusions on whether TMZ should be omitted due to the paucity of survival data among those treated with RT alone.[47] Finally, the Checkmate 498 trial, the largest phase III RCT of unmethylated tumor patients in the literature

that investigated the role of nivolumab + RT compared to TMZ + RT, noted a significant survival benefit for those that received standard-of-care treatment.[48] A mOS of 14.9 months (95% CI: 13.3–16.1) was observed among TMZ + RT control group subjects in contrast to 13.4 months (95% CI: 12.6–14.3) among those that received nivolumab + RT.[48] As the first to prospectively study the omission of TMZ from this population, the investigators concluded that TMZ should continue to be a part of standard care for all glioblastoma patients regardless of p*MGMT* methylation status.[48] The results of the European Organisation for Research and Treatment of Cancer (EORTC) phase III trial of anaplastic glioma without 1p/19q co-deletion (CATNON) (ClinicalTrials.gov identifier: NCT00626990) could clarify the role of TMZ in the treatment of p*MGMT* unmethylated high grade gliomas. Although the latest second interim analysis noted that the benefits of TMZ + RT was limited to IDH1-mutant WHO grade 3/4 gliomas, a conclusive evidence revealing the association with p*MGMT* status has yet to be reported.[49] Until further evidence is unveiled, the latest Society for Neuro-oncology and European Association of Neuro-oncology clinical practice guidelines recommend TMZ for unmethylated tumor patients of favorable age (<70 years) and functional performance, but also advised withholding the agent in circumstances where the risks outweighed its benefits.[3,4]

Several study limitations exist. First, it was based on data from Hong Kong, a south China coastal city, and not from a national registry. Nevertheless, since the latter has yet to be established and the current study is the largest cohort of Chinese glioblastoma patients in the literature, we believe our observations reasonably represent real-world practice. Second, information on progression-free survival and tumor recurrence treatment were not reviewed. Due to the lack of local consensus on second-line systemic therapy we considered the data to be too heterogeneous to draw meaningful conclusions. Third, due to the retrospective nature of the study, tumor biomarker data was incomplete. Only since 2019 was routine *IDH-1* mutation and p*MGMT* methylation testing centrally funded, previously such investigations were carried out by individual institution *ad hoc* requests. Another study limitation was that extent of resection data was primarily drawn from operative record neurosurgical assessments and not by independent evaluations by postoperative day 1 to 3 MRI scans. The major reason why we relied on such assessments was because of the absence of standard imaging protocols in Hong Kong where only 2 of the 7 neurosurgical centers in the city offer early postoperative scanning. Finally, this study defined glioblastoma patients according to the 4th WHO classification and included *IDH-1* mutant tumors. The latest 5th edition recently refined the diagnosis of glioblastoma by adopting a multi-layered integrated approach incorporating new molecular criteria such as *TERT* promoter mutation, *EGFR* amplification or chromosomal 7+ gain/chromosomal 10- loss for *IDH-1* wildtype tumors.[50] Since the majority of diffuse astrocytomas in Hong Kong were not subject to such testing, a proportion of tumors may have been inadvertently excluded from the registry.

Conclusions

This study is the first report revealing the incidence and OS of Chinese glioblastoma patients using a territory-wide population database. The incidence of glioblastoma is relatively low compared to other ethnicities and has remained stable during the study period. We charted the development of neuro-oncological care in Hong Kong. Although the survival of glioblastoma patients in general has not significantly increased, achieving gross total resection and temozolomide chemoradiotherapy can improve outcomes.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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