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Current Cancer Therapy Reviews, 2019, *15*, 1-11

REVIEW ARTICLE

Central Nervous System Neoplasms in Hong Kong - An Inscription of Local Studies

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Abstract: A registry of brain and central nervous system (CNS) tumor patients in Hong Kong comprising of data from both public and private neurosurgical practices (with approximately 98% patients of Chinese origin), suggested geographical or racial variations in disease incidence. The data confers the finding of a comparatively lower incidence rate of meningioma and malignant gliomas as in other parts of Southeast Asia.

With data suggesting epidemiological difference, the treatment response, particularly in high-grade glioma, was studied. Patients suffering from glioblastoma (GBM) in Hong Kong received the standard of care, which involves safe, maximal resection followed by the Stupp regime. 5-aminolevulinic acid (5-ALA)-based fluorescence-guided surgery was found to be feasible and safe to adopt in the treatment of local WHO Grade III & IV gliomas patients. Survival benefit was seen in a group of patients using extended adjuvant temozolomide (TMZ) treatment for newly diagnosed GBM as compared to those treated with the standard 6 cycles. Salvage therapies with either single agent bevacizumab or bevacizumab plus irinotecan appeared to be effective treatment options in Hong Kong patients with recurrent malignant glioma, with a good associated 6-month progression-free survival (PFS) rate which was comparable to previously published overseas data in this disease type in the same overall population.

ARTICLE HISTORY

Received: August 07, 2018
Revised: March 21, 2018
Accepted: August 21, 2018

DOI:
10.2174/1573394715666190126153006

Keywords: Epidemiology, central nervous system, Hong Kong, neurosurgery, extended adjuvant chemotherapy, targeted therapy.

1. INTRODUCTION

This review covers the epidemiology, diagnosis and treatment of primary central nervous system tumors in Hong Kong. The city, with 7 million people, is situated in southern China. Medical care is modern and advanced. The authors also make cross-reference to treatment experiences in the western countries. Different local studies are summarized throughout this review. Since the most common tumor is glioblastoma, it will be discussed in detail below.

2. EPIDEMIOLOGY OF CENTRAL NERVOUS SYSTEM (CNS) TUMOR IN HONG KONG

Epidemiology serves as the foundation and rationality of interventions made in the interest of public health and preventive medicine. The annual incidence of malignant gliomas is approximately 4 in 100,000 people [1, 2]. In 2013, 152,751 people were estimated living with brain and other central nervous system cancer in the United States [3]. Deriving from the data reported in the SEER 2013 [3] and GLOBOCAN 2008 [1], the epidemiology of brain cancer seemingly implies an ethnic variation, with higher prevalence in Caucasians. Asians, especially populations of eastern and southeastern origins, had lower incidences of brain cancer than Caucasians [2]. The data from GLOBOCAN were gathered from cancer registries around the world. There were an estimated 238,000 new cases of brain and CNS tumors diagnosed worldwide in 2008 and the age-standardized rate (ASR) of brain and other CNS cancers was 3.8 in 100,000. European countries, especially the Scandinavian nations, have the highest incidences in the world, with ASRs ranging from 3.82 to 15.17 per 100,000. Amongst the 48 Asian countries, the ASRs range from 0.73 to 5.37 per 100,000. The ASR is reported to be the lowest in the African continent ranging from 0 to 3.85 per 100,000 people [1]. The observation persists in the migrant population as reported in SEER 2013 [3]. Comparing brain cancer incidences obtained from different registries is difficult. Even in regions with

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Table 1. Table excerpted from the Hong Kong Cancer Registry – brain and CNS cancer incidence.

Year	Age 0 to 20-	Age 25- to 40-	Age 45- to 65-	Age 70- to 85+	Cumulative
2004	42	43	80	33	198
2005	37	40	65	34	176
2006	36	43	80	36	195
2007	43	45	83	42	213
2008	37	43	98	38	216
2009	39	26	86	41	192
2010	33	40	94	45	212
2011	37	45	100	39	221
2012	27	46	106	39	218
2013	34	44	115	47	240
Average	37	41	90	40	208

comprehensive cancer registrations, figures on brain and other CNS and intracranial tumors may be affected by variations in pathological diagnosis, under-recording, and inconsistent registration [4].

The Hong Kong Cancer Registry was established in 1963 and has been providing comprehensive data on various cancers in Hong Kong. Nonetheless, the registry collects only data on primary malignant CNS tumors and there is no epidemiological information on benign brain tumors. The average annual incidence of brain cancer is about 208 (Table **1**) [5].

Ho-Cheong reported in Surgical Neurology his experience of intracranial tumors in Hong Kong Chinese patients [6]. Over a two-year period, he documented 56 intracranial surgical biopsies, with glioma being the most commonly observed tumor, followed by meningioma and pituitary tumors [6]. These observations were confirmed by a histological review of CNS tumors in Hong Kong Chinese patients by Ng in the late 1980s [7]. However, a lack of more recent data regarding the incidence of CNS tumors in this patient cohort has meant that researchers have resorted to relying on global population-based epidemiological data.

There was a compelling need to develop a local project that could assist in establishing a more updated and comprehensive intracranial and CNS tumor incidence database in Hong Kong. A contemporary registry of CNS tumor incidences in Hong Kong, comprising data from both public and private neurosurgical practices was initiated to enrich the knowledge of brain tumor epidemiology.

Between July 2008 and June 2009, prospective data were collected from neurosurgical centers across Hong Kong, including seven public centers and eight private clinics. Simple demographic and diagnostic data were collected for patients diagnosed with brain tumor, the diagnosis of which was confirmed either histologically or radiologically. The relevant Institutional Review Board ethics approvals were obtained from each hospital for the study. Identification numbers and names were collected in a partially concealed format. While this system allowed the removal of duplicated data, it limited the collection of detailed patient information. Data input and analyses were performed using SPSS version 14.0 for Windows (SPSS, Inc., Chicago, IL).

Over the one-year assessment period, a total of 1,025 newly diagnosed cases of spinal and intracranial tumors were identified, with a slight female predominance (55% vs. 45%) and 97.8% of patients were of Chinese origin. There were 759 primary CNS tumors of which 618 (81.4%) were benign in nature and 141 (18.6%) were malignant tumors. Based on a total Hong Kong population of seven million, the estimated spinal and intracranial tumor incidences (of any type) were 14.7 per 100,000 per year and the incidence of primary CNS tumors was 10.8 per 100,000 per year. Subtype classification of these tumors is provided in Table **2**.

The incidence of meningioma per annum was 3.5 per 100,000 and within the category 96.3% was WHO Grade I meningioma, 2.8% was WHO Grade II meningioma, and 0.8% was WHO Grade III meningioma. Female had a higher incidence of meningioma than male and the phenomenon spanned across all age groups.

Data of 70 cases of high-grade gliomas (WHO Grade III and IV) were collected over the year. The incidence of high-grade gliomas was 1 in 100,000 per year. The most frequently seen glioma subtype in Hong Kong was glioblastoma (GBM). 52 cases of this WHO Grade IV glioma were observed. This figure comprised 42% of all glioma cases and 5% of all brain tumor cases. The incidence of GBM was <1 in 100,000 per year. High-grade gliomas were most prevalent in the age group ranged between 45 to 64 (Fig. **1**).

In the pediatric group (age <18), there were a total of 36 newly diagnosed brain tumor cases with confirmed diagnoses during the study period. The most frequently seen tumor type in the pediatric group was glioma, followed by germ cell tumor, 15 cases (42%) and 10 cases (28%), respectively (Table **3**).

Table 2. Incidence of brain tumor subtypes in the registry.

	Frequency	%
Meningeal tumors	246	23.9
Cerebral metastases	210	20.4
Pituitary tumors (pituitary adenoma, chromophobe adenoma)	171	16.6
Glioma*	124	12.0
Tumors of peripheral nerves/cranial nerves	93	9.0
Other tumors	57	5.5
Unconfirmed	53	5.1
Tumors of the sellar region	16	1.6
Germ cell tumors	15	1.5
Lymphomas and hemopoietic neoplasms	13	1.3
Embryonal tumors	8	0.8
Pineal parenchymal tumors	7	0.7
Neuronal and mixed neuronal-glial tumors	6	0.6
Choroid plexus tumors	3	0.3
Syndromal	3	0.3
Total	**1,025**	**100.0**

** Including astrocytic tumors, oligodendroglial tumors and mixed gliomas, and ependymal tumors*

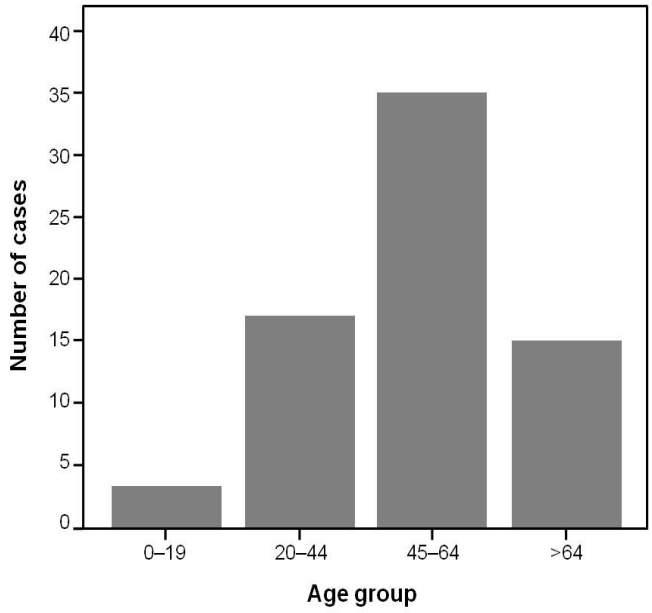

Fig. (1). Incidence rates of high-grade glioma by age group.

Data for pediatric brain tumor incidence from this study were comparable with figures obtained from the Hong Kong Pediatric Hematology/Oncology Study Group [8] and Hong Kong Cancer Registry [9], demonstrating a similarly high incidence of germ cell tumors in the pediatric group (data not shown).

Table 3. Data of CNS tumors in the pediatric group (age<18).

	Frequency	%
Glioma	19	35.8
Choroid plexus tumors	3	5.6
Neuronal and mixed neuronal-glial tumors	3	5.6
Pineal parenchymal tumors	3	5.6
Embryonal tumors	4	7.5
Pituitary tumors	2	3.8
Tumors of peripheral nerves/cranial nerves	3	5.6
Lymphomas and haemopoietic neoplasms	2	3.8
Germ cell tumors	10	18.9
Tumor of sellar region	1	1.9
Syndromal	3	5.6
Total	**53**	**100**

Data were compared with figures published in 2006 by The Hong Kong Cancer Registry [9] which solely collected data on primary malignant tumors of the CNS (Table **4**).

Table 4. Frequency of CNS tumor subtypes in Hong Kong Chinese patients.

	HK Cancer Registry (2006)	HKNS Registry (2008-9)
Astrocytic tumors	113	89
Oligodendroglial tumors and mixed gliomas	19	19
Ependymal tumors	17	14
Other gliomas	7	2
Medulloblastoma	9	8
Total	**165**	**132**

HK: Hong Kong; HKNS: Hong Kong Neurosurgery

The annual incidence rates of malignant gliomas and meningiomas in the Hong Kong population of Chinese origin are comparatively lower than the reported US incidence rates. The data suggests genetic difference, risk factors exposure, geographical, and racial benefactions in the incidence of brain tumors.

The resulting data reflected the incidence across the one-year study period (2008–9). Future effort in continuing this kind of study will require collaboration with oncologists, physicians, radiologists, hospital statisticians, and epidemiologists in Hong Kong. Collection of more detailed demographic data and risk factors analyses would be the forthcoming aim. While this study provides an important foundation for further research and health care planning, additional refinement and data collection are needed in order to reveal the true epidemiology of brain tumors in Hong Kong.

3. MANAGEMENT OF MALIGNANT PRIMARY CENTRAL NERVOUS SYSTEM TUMORS IN HONG KONG

3.1. Diagnosis and Imaging

Clinically, patients with malignant glioma mostly present with headaches, seizures, focal neurological deficits or cognitive dysfunctions. Symptoms and signs related to malignant glioma can be categorically divided into two groups:

[1] Symptoms related to the elevated intracranial pressure caused by the mass of the tumor

[2] Site-specific symptoms relating to the location of the tumor.

Raised intracranial pressure can cause headache, nausea, vomiting, drowsiness, visual blurring, papilledema, and nuchal rigidity. Site-specific clinical features vary by tumor location, and may include motor, sensory, visual, speech, and cognitive or behavioral disturbances.

By the time of diagnosis, about 70% of patients would complain of headache, ranking it the most common symptom [10]. The incidence of epilepsy in patients with GBM ranges between 30% and 62% in different studies [11, 12]. Around 29% of malignant astrocytoma patients present with seizures. The rate of seizure occurrence is less observed in oligodendroglioma, ependymoma or other types of gliomas [13]. Site-specific symptoms are the consequence of either irritation or infiltration by the tumor into the eloquent areas of the brain. Focal neurological deficits are more frequently seen in malignant astrocytomas than low-grade gliomas [13]. In the study by Kerkhof *et al.* on malignant gliomas, factors associated with pre-operative seizures are anaplastic astrocytoma, tumor in temporal lobe, and cortical location [12].

3.2. Computer Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT) Scan

In the medical setting of modern Hong Kong, the availability of CT and MRI has majorly facilitated the diagnosis of CNS tumors. Since the introduction of these imaging scans, there are more incidental findings of asymptomatic brain tumors. CT remains the most widely used modality of neuro-imaging for the diagnosis of brain tumors. CT is good for detecting calcification or bony abnormality. Tumors with different intensities can be differentiated from brain parenchyma using CT. Malignant glioma usually appears as a heterogeneous mass with poorly defined margin on non-enhanced CT scans, often exhibiting a significant mass effect and edema. On contrast-enhanced CT scans, there is a possible ring or solid enhancement. Hence, due to the limitation in resolution and sensitivity of CT, MRI has become more popular in the diagnosis and monitoring of brain tumor, especially glioma.

Malignant gliomas on MRI mostly appear as lesions with irregular and indistinct borders, with heterogeneous signals on T1W and T2W sequences. Diffusion on diffusion-weighted image (DWI) is restricted due to the dense cellularity of the tumor. Gadolinium enhancement may be homogenous or heterogeneous, although some high-grade gliomas may not have gadolinium enhancement. The presence of necrosis with irregular peripheral enhancement is suggestive of the tumor being a GBM. Fluid-attenuated inversion recovery (FLAIR) is an MRI sequence with an invesion recovery set to null fluids. For example, it can be used in brain imaging to suppress cerebrospinal fluid (CSF) effects on the image, so as to bring out the periventricular hyperintense lesions. T2W and FLAIR sequences may also reveal the infiltrativeness, vasogenic edema and inflammation generated by malignant glioma. The availability of

Magnetic Resonance Spectroscopy (MRS) and MR perfusion gives additional help in distinguishing demyelinating disease, post treatment effect from active glioma.

PET is a nuclear medicine imaging technique that provides metabolic tumor studies. Various substances can be labeled with a positron-emitting isotope, for example 18-fluoro-2-deoxyglucose that images glucose metabolism and 11-carbon-methionine which images deoxyribonucleic acid (DNA) metabolism. Tumor grading can be identified by the proportional increase in the uptake of isotope. An 18-fluoro-2-deoxyglucose PET scan with hypermetabolic "hot" spots suggests high-grade astrocytoma and helps distinguish non-enhancing high-grade gliomas on MRI. PET scans are also useful in differentiating radiation necrosis from recurrent tumor.

4. TREATMENT

4.1. For Newly Diagnosed High-Grade Glioma

Multidisciplinary management is also the key approach to the treatment of both newly diagnosed and recurrent malignant gliomas. Patients with newly diagnosed malignant gliomas are recommended to undergo maximal surgical excision to achieve the purpose of both tissue histopathological diagnosis and cytoreduction. Aside from histopathological study, molecular genetic analyses (e.g. MGMT methylation, IDH-1/2 mutation, 1p19q co-deletion, p53, ATRX, BRAF mutation) have also become standard investigations in all major histopathology laboratories. The O^6-methylguanine-DNA-methyltransferase (MGMT) and isocitrate dehydrogenase 1 or 2 are available earlier. Adenosine triphosphate (ATP)-dependent helicase transcriptional regular (ATRX), an X-linked helicase II, becomes available recently.

For WHO Grade III and Grade IV tumors, the globally adopted "Stupp Regime Adjuvant Therapy" [14] is followed after surgery. The treatment includes concurrent chemo-irradiation comprising of 6 weeks of fractionated radiotherapy (60 Gy, 30 to 33 fractions of 1.8 to 2 Gy) and concomitant administration of the oral chemotherapeutic agent temozolomide (TMZ) (75 mg/m^2/day). Patients then take a 4-week break before entering the maintenance phase. During this phase, TMZ 150 to 200 mg/ m^2/day is taken over 5 days in each 28-day cycle for 6 cycles.

4.2. For Recurrent High-Grade Glioma

Surgery is still a preferable treatment of choice, if feasible, for a patient with recurrent high-grade glioma. In a study of 22 Chinese patients with recurrent malignant glioma (13 GBM, 9 anaplastic glioma) treated with TMZ, the 6-month PFS rates were 21% and 46% for GBM and anaplastic glioma, respectively; mean PFS across glioma subtypes was 7.2 months [15]. These data indicate that response to treatment in patients with recurrent glioma is similar regardless of ethnicity. Bevacizumab was approved for use as a single-agent in patients with relapsed GBM by the Department of Health in Hong Kong in September 2009. Bevacizumab and irinotecan or single agent bevacizumab were also used in Hong Kong for patients with recurrent disease. The drug regimes were administered until disease progression or discontinuation due to complications, according to a schedule adapted from Vredenburgh [16]. Bevacizumab (10 mg/kg) and irinotecan (125 mg/m^2 [dose modified to 340 mg/m^2 for those taking enzyme-inducing antiepileptic drugs]) were both administered as an intravenous (i.v.) infusion on day 1 of a 14-day schedule. Irinotecan (i.v. over 90 minutes) was administered before bevacizumab (i.v. over 30 minutes). Single-agent bevacizumab regiment was adapted from the randomized controlled trial by Friedman [17]. Bevacizumab (10 mg/kg) was administered as an i.v. infusion on day 1 of a 14-day schedule.

4.3. Local 5-Aminolevulinic Acid (5-ALA) Surgery Data

Complete resection of over 98% of glioma has been shown to improve median survival compared with partial resection [18]. Thus far in Hong Kong, intraoperative MRI is not available. The introduction of fluorescence-guided resection using 5-ALA has enhanced the practice of glioma surgery in terms of the extent of resection [21]. 5-ALA is a natural precursor in heme synthesis. It is preferentially accumulated in malignant cancer cells, where it would be converted into protoporphyrin IX. Under specific excitation lighting within the violet-blue spectrum (440 nm), protoporphyrin IX would emit red fluorescence (550-750 nm) that can be visualized with specialized filters fitted onto an operating microscope [19]. Tumor tissue, which may otherwise be indistinguishable from normal brain tissues, can therefore be identified and removed with increased accuracy.

A retrospective study data on patients who underwent 5-ALA-assisted resections of malignant gliomas at Queen Mary Hospital between March and November 2011 was carried out. Correlations between the intraoperative emission of fluorescence intensity and the pathological findings (according to World Health Organization 2007 diagnostic criteria) of the resected lesions were made. The extent of the surgical resection was assessed by MRI imaging performed within 48 hours after surgery. Residual lesions were defined by the presence of contrast-enhancing lesions on T1-weighted MRI studies. Perioperative complications, operating time, patient's functional status as determined by the Karnofsky Performance Score (KPS), serological changes and the length of stay in the hospital were also reviewed. Statistical and survival analysis was performed in SPSS version 19.0 for Windows (SPSS, Inc., Armonk, NY: IBM Corp).

Ten procedures were performed as one patient underwent two 5-ALA-assisted resections. Two patients underwent awake-craniotomy together with the assistance of 5-ALA for tumor removal. Of the 10 surgical procedures only 4 were primary, virgin surgeries and the rest were for suspected, residual or recurrent malignant tumor. The demographic, histopathology, tumor location, presence of fluorescence and its intensity were summarized (Table **5**).

Of the 10 resected lesions, 8 (80%) produced fluorescence during surgery. The fluorescent intensity appeared to have a good correlation with the grading of the tumors in this small cohort of patients. In Grade III glioma, there were either no fluorescence or only revealed mild intensity when compared to Grade IV tumors. One of the 8 fluorescent lesions was non-neoplastic in nature, yielding an overall false-

Table 5. Patient demographic, tumor types, fluorescence and pathological findings.

Patient	Sex	Age	Surgical Procedure	Pathology / Location / MGMT Methylation Status	Fluorescence	Fluorescence Intensity
1	M	53	Primary surgery	GBM, eloquent, MGMT meth -ve	Yes	Intense
2	M	68	Primary surgery	GBM, non-eloquent, MGMT meth +ve	Yes	Intense
3	F	36	Primary surgery, motor mapping	Anaplastic oligodendroglioma, eloquent, MGMT meth +ve	No	
4	M	53	Second surgery	Gliosis, eloquent	Yes	Mildly intense
			Third surgery, awake craniotomy	Recurrent GBM, Eloquent, MGMT meth -ve	Yes	Intense
5	F	53	Second surgery	Anaplastic astrocytoma, eloquent MGMT meth -ve	No	
6	M	55	Second surgery	GBM, eloquent MGMT meth –ve	Yes	Intense
7	M	34	Second surgery	Anaplastic oligoastrocytoma, non-eloquent, MGMT meth +ve	Yes	Mildly intense
8	M	54	Third Surgery	Anaplastic oligodendroglioma, non-eloquent, MGMT meth +ve	Yes	Mildly intense
9	M	81	Primary Surgery	Anaplastic oligoastrocytoma, MGMT meth +ve	Yes	Mildly intense

F, female; GMB, glioblastoma; M, male; MGMT meth: O^6-methylguanine-DNA-methyltransferase methylation

positive rate of 12.5%. Two non-fluorescent lesions were malignant (WHO grade III) in nature, giving an overall false-negative rate of 25%. The overall sensitivity of 5-ALA fluorescence for malignant gliomas was 77.8%. The overall accuracy was 70%.

The majority (78%) of the tumors were located in eloquent areas. Based on post-operative MRI assessment performed within 24 hours after the 10 surgical procedures, there were 4 gross total resections (GTR), 5 near total resections (NTR) and 1 subtotal resection (STR). Overall, 90% of the resection procedures were able to achieve a satisfactory tumor bulk removal when 5-ALA was used as a surgical adjunct and improved the rate of gross total resection.

There was no peri-operative mortality. None of the patients developed allergic or dermatological complications. In the 10 post-operative blood-screening procedures, 8 (80%) and 2 (20%) patients had a transient increase in blood leucocyte counts and liver parenchymal enzymes, respectively. These were not clinically significant and resolved after three to four days. When compared to their pre-operative functional status, 3 (30%) had deteriorated functional status after the surgery but 2 patients were able to recover after rehabilitation and one remained functionally poor due to residual disease. 78% of the patients maintained a good functional status (KPS score 80-100%) 3 months after surgery.

Table 6. Comparison between findings of the Hong Kong data and previously reported studies.

	Pathology	Patient	Biopsy	Sensi-tivity	Speci-ficity	Accuracy	PPV	NPV	Complete Resection
Stummer, 1998 [20]	GBM	9	89	85%	100%	90%	100%	75%	77%
Stummer, 2000 [21]	GBM	52	267	89%	96%	90%	99.5%	50%	63%
Nabavi, 2009 [22]	Recurrent Grade III/IV glioma	36	354	N/A	N/A	N/A	96.6%	N/A	19.4%
Widhalm, 2010 [23]	Grade II/III glioma	17	N/A	89%	100%	94%	100%	89%	N/A
Roberts, 2012 [24]	GBM	11	124	75%	71%	74%	95%	26%	N/A
HK data	Malignant brain tumors	9	10	77.8%	N/A	70%	87.5%	N/A	90%

PPV: positive predictive value; NPV: negative predictive value; GBM: glioblastoma multiforme WHO grade IV; N/A: not available; HK: Hong Kong

The median progression-free survival (PFS) for this group of patients with malignant glioma was 10 months and the median overall survival (OS) was 20 months. There were 4 patients with GBM and the median PFS was 5.5 months and median OS was 15 months. Five patients with WHO Grade III tumors thrived significantly better. Their median PFS was 30.5 months and median OS was 41 months.

Our study demonstrated that 5-ALA has good specificity in GBM and the experience indicated that 5-ALA-based fluorescence-guided surgery was feasible and safe to adopt in the treatment of malignant glioma (Table **6**). This surgical adjunct also helped the majority of the procedures to achieve a satisfactory extent of removal. To further extrapolate its usage in resection of tumor in eloquent areas, other intraoperative functional mapping techniques, when used together with 5-ALA, are useful in ensuring the preservation of neurological function. More importantly, a small group of patients who may likely benefit from using this agent was identified. The subgroup analysis showed significant disease-free survival after 5-ALA guided resection in WHO Grade III gliomas with positive MGMT methylation status.

4.4. Extended Temozolomide for Newly-diagnosed Glioblastoma

For newly diagnosed high-grade glioma, after surgery, the Stupp regime is the standard treatment in oncology centres around Hong Kong. In other countries, the long-term administration of adjuvant TMZ is commonly practiced in many institutions for patients who have good tolerance of chemotherapy and have stable disease [25-28]. This practice was also adopted in a tertiary institution in Hong Kong where the median PFS was 15.3 months and OS was 19.4 months for 136 patients with GBM. A retrospective analysis (unpublished) was conducted with data collected from years 2008 to 2013 using SPSS version 22.0 for Windows (SPSS, Inc., Armonk, NY: IBM Corp). There were 25 patients who received adjuvant TMZ, of whom 11 had more than 6 cycles of adjuvant TMZ and 14 had 6 cycles only. The group of patients who received more than 6 cycles had median PFS of 22 months and median OS of 25 months. The group that received 6 cycles had median PFS of 13 months and median OS of 16 months. These data suggest that extended adjuvant TMZ (*i.e.*, more than six cycles) treatment may confer survival benefit as compared to the standard 6 cycles. A local published study reported progression-free survival in patients received extended treatment [29]. The secondary analysis of EORTC and NRG Oncology/RTOG also showed increased progression-free survival, particularly in patients with MGMT-methylation positive tumors [30]. There was seemingly a subset of patients with malignant gliomas who had survival benefit with extended adjuvant TMZ. Extended adjuvant TMZ is not a definite standard of care but seems to be a safe and feasible treatment option for a subgroup of patients with newly diagnosed glioblastoma.

4.5. Targeted Therapy in Recurrent High-Grade Glioma

Response to temozolomide in patients with recurrent glioma is generally poor; in a Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma 6-month PFS was 23.9% and 35.7% for patients with GBM and anaplastic glioma, respectively [31]. In a study of 22 Chinese patients with recurrent malignant glioma (13 GBM, 9 anaplastic glioma) treated with temozolomide, the 6-month PFS rates were 21% and 46% for GBM and anaplastic glioma, respectively; mean PFS across glioma subtypes was 7.2 months [15]. These data indicate that response to treatment in patients with recurrent glioma is similar regardless of ethnicity. The safety profile of bevacizumab plus chemotherapy in the Chinese population was consistent with that reported for the global SAiL population [32] and AVAiL trials [33]. These data indicate that good clinical responses to bevacizumab should be seen in the local Hong Kong patients. The objective of this study is to review the local expe-

Table 7. Patient characteristics at baseline: PCV, procarbazine, CCNU and vincristine.

Patient Characteristic	Patients – Bevacizumab + Chemotherapy (n=14)	Patients – Single-agent Bevacizumab (n=11)
Age (years); median (range)	50 (18-69)	50 (21-58)
Sex; male/female	11/3	5/6
Histology		
Glioblastoma multiforme	11	10
Anaplastic astrocytoma	1	1
Anaplasic oligodendroglioma	1	
Anaplasic oligoastrocytoma	1	
Tumor location		
Eloquent cortex	13	**7**
Non-eloquent	8	**4**
MGMT methylation status		
Positive	2	**2**
Negative	8	**8**
Unknown	3	**1**
Prior salvage treatment		
Surgery	14	**11**
1 procedure	5	**8**
2 procedures	6	**2**
> 3 procedures	3	**1**
Prior chemotherapy		
Stupp regime (completed)	12 (3)	**11**
PCV	4	**0**

rience of bevacizumab as an adjuvant treatment in recurrent malignant glioma in patients, with Chinese ethnicity being the majority and how this compares to previous studies in the global population.

Between November 2005 and November 2009, 14 Hong Kong Chinese patients presenting with recurrent glioma at three centers (two private clinics and a public hospital) were treated with bevacizumab plus irinotecan, as an off-label drug prior to this approval. Also between April 2011 to December 2013, 11 Hong Kong patients received single agent bevacizumab (four public hospitals). In total, 25 patients who received treatment involving bevacizumab were included in the study.

Patients were confirmed to have Histological classification of high-grade malignant gliomas ~~was performed~~ according to the 2007 WHO brain tumor classification system. Patients underwent resection and had cranial lesions confirmed as high-grade malignant glioma by a certified pathologist. Patients received primary adjuvant radiotherapy and chemotherapy after surgery. Bevacizumab and irinotecan or single agent bevacizumab were administered until disease progression or discontinuation due to complications, according to a schedule adapted from Vredenburgh[16]. Single-agent bevacizumab regiment was adapted from the randomized controlled trial by Friedman [17]. Post-contrast-enhanced MRI reports before surgery, post surgery, after initial treatment and during treatment with bevacizumab and irinotecan or single agent bevacizumab were evaluated, with the exact size of tumor recorded according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Additional information from other imaging sequences including T2-weighted fast spin echo and axial T2 FLAIR were taken into account when evaluating the response to bevacizumab and irinotecan. Radiologists who reviewed the images were all blinded to clinical outcome.Survival analyses were conducted using life tables and survival plots. The endpoints evaluated were 6-month PFS, overall response rate (ORR) and overall survival. Adverse events (AEs) were recorded and graded according to the National Cancer Institute (NCI)

Table 8. Treatment response.

-	Bevacizumab +Chemotherapy (n=14)	Single-agent Bevacizumab (n=11)
Overall response rate n (%)	12 (85.7)	7 (63.6%)
Complete response n (%)	4 (28.6)	2 (18.2)
Partial response n (%)	8 (57.1)	5(45.5%)
Stable disease n (%)	0	0
Progressive disease n (%)	1 (7.1)	4(36.4)
Unknown response n (%)	1 (7.1)	0
Median PFS (months)	6.0	6.0

n, number; PFS, progression free survival

Table 9. Most commonly observed adverse events during the bevacizumab and irinotecan treatment period.

Adverse Event	Bevacizumab + Chemotherapy (n=14)	Single-agent Bevacizumab (n=11)
Hematologic complication	5	2
Pulmonary embolism	2	2
Hypertension	2	2
Proteinuria	2	2

Table 10. High-grade glioma – efficacy data compared with historic and overseas studies.

-	Chemotherapy ~~[2]~~	Bevacizumab [Overseas Publication]	Bevacizumab + Irinotecan [Local Study]
Response Rate	5-10% [36]	63% [16]	85.7% [35]
PFS-6 months	10-24% [36]	42.6 – 50.3% [16]	63.6% [35]

PFS, progression free survival; ref, references.

Common Terminology Criteria for Adverse Events version 3.0 (CTCAE). Any laboratory result anomaly fulfilling the criteria for a serious adverse event was also documented.

Amongst those patients who received bevacizumab and irinotecan, many had multifocal tumors (8 out of 14) and only two patients in the single-agent bevacizumab group had multifocal tumors. All patients were over 18 years of age; patient characteristics are given in Table **7**. No patients were lost to follow-up.

Radiological response was observed in 19 patients in the combination of both groups. Response rate for the overall population was 76%. Median PFS for both groups was 6.0 months. The median OS were 17.5 months and 12.5 months for bevacizumab + chemotherapy group and single agent bevacizumab group (range from 3 to 61 months), respectively (Table **8**).

The most commonly observed adverse events (AEs) during salvage therapy with bevacizumab plus irinotecan were hematological, with 5 patients reporting Grade 2/3 AEs according to CTCAE. Pulmonary embolism occurred in two patients, one of which resulted in death. Other common bevacizumab-related side effects such as hypertension and proteinuria were also noted (Table **9**). Intracranial hemorrhage was not detected in any of the 25 patients treated.

Previous data in metastatic/recurrent [34] or previously untreated cancers [34] have shown that bevacizumab is well tolerated in Asian patients and that no racial difference exists in the pharmacokinetics of the drug. This case series reported the first use of bevacizumab in Asian patients with glioma and showed that good objective responses to bevacizumab were achieved. The 6-month PFSs observed in both the local and overseas case series were comparable in this disease type in the overall population [16, 17, 35] (Table **10**).

Salvage therapy with bevacizumab (with or without chemotherapy) appeared to be an effective treatment option in Hong Kong patients with recurrent malignant glioma, with a good associated 6-month PFS rate.

4.6. Other Treatments for recurrent CNS Tumors

Reirradiation of the brain has been reported by some authors [35-37]. After 60 Gy/30f to a surgical cavity in the left temporal lobe, Patel *et al* treated the adjacent recurrence of 13 cc to 18 Gy (90% isodose covering). The National Comprehensive Cancer Network recommends clinical trial enrollment, palliative care, surgery, reirradiation and alternating electric fields [38]. Reirradiation of spinal cord tumors is safe. Procedures and guidelines have been documented by Saghal, *et al*. [39-42].

CONCLUSIONS AND FUTURE DIRECTION

Management for newly diagnosed high-grade glioma in Hong Kong largely follows the protocol, which involves safe maximal surgical resection, concurrent chemotherapy following by adjuvant chemotherapy. Our local retrospective analysis suggested extended adjuvant TMZ (i.e., more than six cycles) treatment conferred survival advantage and could be considered in future studies or trials with newly diagnosed GBM.

The local Hong Kong experiences indicated that 5-ALA-based fluorescence-guided surgery was feasible and safe to adopt in the local ethnic Chinese population. Although the addition of bevacizumab to the Stupp regime did not show benefit in OS of newly diagnosed glioblastoma, bevacizumab is still one of the treatments of choice for recurrent malignant glioma. Using bevacizumab was at least as effective at treating Chinese patients with recurrent glioma as previously reported overseas clinical trials. Bevacizumab is well tolerated in Chinese patients and no racial difference exists in the pharmacokinetics of the drug. Bevacizumab has already been approved by the Department of Health in Hong Kong since September 2009, for use as a single-agent in patients with relapsed GBM; it was, however, an off-label drug up until the present date in Hong Kong.

Currently, there is no standard treatment for recurrent malignant glioma, and clinicians may still have to rely on repeated surgeries and, perhaps, bevacizumab in prolonging the survival of patients with the recurrent disease. More trials on different systemic therapies are needed in the future.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Appreciations to the Hong Kong Neurosurgical Society, Hong Kong Cancer Registry, Hospital Authority, Kwong Wah Hospital, Pamela Youde Eastern Hospital, Princess Margaret Hospital, Prince of Wales Hospital, Queen Elizabeth Hospital, Queen Mary Hospital, Tuen Mun Hospital and Hong Kong Pediatric Hematology/ Oncology Study Group.

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