Comparative Parameters of Occult and Multiple Brain Tumors In Human: The Implication for Therapy

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Research article

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Abstract

Background

Brain cancer treatment is a difficult task, because of complex nature of physico-chemical properties of brain, central nervous system (cns) acting drugs and drug carriers.

Methods

In view of this, literatures were searched with a view to assessing comparative mathematical parameters of occult and multiple primary brain tumors and their therapeutic outcomes. A total of thirteen patients comprised of eight males and five females who had suffered either occult or multiple brain tumors were used for the study. Tumor parameters and their therapeutic prognoses were mathematically determined. The data were analyzed using a modified Kaplan-Meier method at 5 % level of significance.

Results

Findings have shown that occult tumors such as meningiosarcoma (65.4cm^3), teratoma (268 cm^3), solitary brain tumor (20.6–22.4 cm^3) and gliosarcoma (31.1 cm^3) as well as multiple primary brain tumors; meningioma/diffuse astrocytoma (47.7 cm^3), glioblastoma multiforme/pituitary adenoma (164. 59 cm^3) and planum sphenoidale meningioma/pituitary adenoma (26.52 cm^3) are deadly. However solitary brain tumor (4.2 cm^3), glioblastoma multiforme/pituitary adenoma (12.77 cm^3) and multimeningioma/pituitary adenoma (0.70 cm^3) have high survival rate. Generally tumor weight (4.2–144.0 g), tumor density (0.24–0.96), total population of tumor cells (9.5 x 10^8-2.5 x 10^{11}, rate of tumor cell migration (1.10–48.0 cm^2/yr) and tumor radius (0.55-4.0 cm) are relatively moderate to very high, signifying that occult brain tumors may generate faster and may be more difficult to treat chemotherapeutically, radiotherapeutically, immunologically and surgically. Brain tumors affect male and female of 2–79 years old.

Conclusions

The locations of tumors are parietal, temporal, frontal, thalamic, frontoparietal, stellar, and planum sphenoidale lobes. Both occult and multiple brain tumors are diagnosed when all forms of therapy would have been useless.

Introduction

Brain cancers are difficult to treat because of very high life-threatening toxicity signs associated with the drugs [1].Examples of brain cancers are astrocytoma, meningioma, oligodendroglioma, medulloblastoma, ependymoma, brain stem glioma [2], glioblastoma, diverse brain tumors and craniopharyngioma [3]. Acute hemiparesis is one of the signs of primary or metasatic brain tumor [4]. Control of local brain tumor is highly diffiduclt and the patients die of tumor recurrence and progression [5]. Medulloblastoma yields to chemotherapy unlike high-grade cortical or brainstem gliomas[6]. The incidence of brain tumors is lower in Iran as compared to other countries of the world [7]. Hyperspectral imaging is a suitable technique used for cetectum of high-grade tumors from pathological slides [8]. Gliomas constitute > 50% of all brain tumors. Medical imaging has increased the diagnosis of gliomas but not the degree of diffuse invasion of the tumor cells [9].Glioma of 20cm^3 and 6 cm in diameter if left untreated for up to 7.2 years could kill [10]. The dose rate for bleomycin is 10 iu/m^2 [1], for 3 days thereafter 10 units/m^2 weekly with maximum cumulative dose of 200 units/m^2 [11], indicating that mathematical parameters of tumors could be used as indices of therapeutic success or failure [12]. This is very important in management of brain tumor, because association of maturation of white matter with development of cognitive function in children [13], could be affected by tumor of white matter. Hence there is need to assess mathematically the parameters of brain tumors with a view to determining their therapeutic outcomes [14]. However comparative parameters of tumor kinetics need to be studied with a view to determining their pathogenesis, diagnosis and therapeutic implications in young and adult humans.

Materials And Methods

Literatures were searched for formulas used in calculation of tumor parameters. Used for the study are the reported cases of occult brain tumors/cancers such as solitary brain cancer of left and right parietal lobe, meningiosarcoma of right fronto-parietal lobe, diffused teratoma, brain cancer of right temporal lobe, solitary cancer of right frontal lobe, gliosarcoma of right thalamic region and brain tumor of right fronto-temporal lobe as well as diverse brain tumors; glioblastoma multiforme, meningioma and planum sphenoidale meningioma in 13 human comprised 7 males and 6 females of 2–79 years, and their treatments using bleomycin were re-assessed using the formulas [1, 3, 10–12, 14, 15]. Rate of change of tumor cell density = Diffusion of turnover cells (D) in mm^2/yr and net proliferation rate (p) per yr of the cancer cells were calculated. Density of tumor cells that will cause diffusion is 2–4000 cells/mm^3. The time from diagnosis to death of tumors in grey matter is 8 months, whereas that of white matter is 5 months, but radius (r) = maximum gradient tumor width. Tumor volume, tumor weight, tumor density, tumor radius, proliferated total cells and rate of

tumor cell migration were calculated [1, 10, 12, 15]. The velocity of 5.8 mm per year is spontaneous and after 7.2 years the velocity becomes 41. 8 mm [16].The velocity of radial growth was calculated using the formula below. Velocity V^2 = 4DP, whereas D = rate of proliferation (m^2/yr) [17]. Tumor doubling time is 60–90 days [18], whereas 1 g of tumor mass is 10^9 cells = 30 doubling time; Tumor weight = Tumor length x Tumor $width^2/2$ and Tumor volume = π x 3.14159 x $r^{3,}$ whereas r = radius [12].

Results

The mathematical parameters of occult primary tumors are presented in Table 1.Tumor volume of 4.2–268 cm^3, tumor weight (1.0-144g), density (0.24–0.61), total population of tumor cells (1.7 x 10^9-2.5 x 10^{11}, tumor radius (1.0–4.0 cm) and rate of tumor migration have been calculated for solitary brain cancer, meningiosarcoma, teratoma, brain cancer, and gliosarcoma (Table 1).However tumor volume (0.70-164.59 cm^3), tumor weight (0.55–99.14 g), tumor density (0.50–0.96), total population of tumor cells (9.5 x 10^8-1.7 x 10^{11}), radius (0.55-4.0 cm) and rate of migration (1.10-36.72 cm^3/yr) have been calculated for multiple primary brain tumors such as meningioma/diffuse astrocytoma, glioblastoma multiforme/pituitary adenoma, planum sphenoidale meningioma/pituitary adenoma and multimeningioma/pituitary adenoma.

Table 1
Mathematical parameters of occult primary brain tumors in human

Tumour type	Sex	Age	Location	Dimension (cm)	TV (cm^3)	TW (g)	Density	Radius (cm)	TP	RM	Comment(s)
Solitary brain cancer	M	48	Left Parietal lobe	2x1x1	4.2	1.0	0.24	1.0	1.7 x 10^9	2.0	High survival
Meningiosareoma	F	58	Right front-parietal	5x4	65.4	40.0	0.61	2.5	6.9 x 10^{10}	20.0	Dead
Teratoma	F	2	Diffused	8x6x5	268	144.0	0.54	4.0	2.5 x 10^{11}	48.0	Dead
Solitary brain cancer	M	69	Right parietal lobe	3.4	20.6	4.91	0.24	1.7	8.5 x 10^9	11.56	Dead
Brain cancer	F	52	Right temporal lobe	4	33.5	8.0	0.24	2.0	1.4 x 10^{10}	16.0	Dead
Solitary brain cancer	M	79	Right frontal tumor	3.5	22.4	5.36	0.24	1.75	9.2 x 10^9	12.25	Dead
Gliosarcoma	M	57	Right thalamic region	3.3x3.1x3.9	31.1	18.74	0.60	1.95	3.2 x 10^{10}	12.87	Dead
Brain tumor	M	41	Right front-temp	5x4	65.4	40.0	0.61	2.5	6.9 x10^{10}	20.0	Dead
Keys: TV = Tumor volume; TW = Tumor weight; TP = Total proliferation; RM = Rate of migration											

Discussion

The higher tumor volume (4.2–268 cm^3) calculated for occult primary tumors as compared with that of multiple brain tumors with diverse origin (0.70–164. 59 cm^3) shows that occult tumor is deadlier and more proliferative. Brain tumor cell of less than 2cm can be treated using chemotherapy [19]. Medulloblastoma can affect children of greater than 3-years. Pediatric tumors, global and neuronal are more sensitive to chemotherapy [20]. Lomustine is not effective in the treatment of brain tumors hence may not be effective in human. Therefore there is need for standardized design and treatment outcomes for brain tumors [21]. Elderly patients with malignant astrocytoma's received limited treatments which are correlated with survival variation, suggesting that in clinical neurooncology, patient age is associated with lack of effective therapy and worse prognosis [22]. Diagnostic and treatment modalities of brain tumors have been advanced by neuroimaging [23] despite the increased incidence in all the age groups especially the older adults [24]. Strict adherence to treatment protocol of brain tumors in pregnant allow term delivery via vagina [25]. The most frequent brain tumors are gliomas, therefore optimal treatments should be standardized and individualized [26]. Although, chemotherapy plays a significant role in childhood in edulloblastoma, low-grade gliomas, and high-grade gliomas, others such as a typical teratoid tumors, brainstem gliomas, malignant gliomas and malignant infantile tumors remain therapeutic dilemmas [27]. Early detection of gliobhlastoma multiform has little effect on survival of elderly patients [28]. Patients with tumor volume less than 20 cm^3 have lower risk of death than the patients with tumor volume higher or equal to 20 cm^3 [29]. ZIC_1 and ZIC_2 are markers of meningiomas while ZIC_4 is for medulloblastoma and may reflect properties of tumor tissue [30] invariably determining the mechanisms of action of their anticancer drugs. However, intracranial hemorrhage is common with patients of brain tumors [31]. Tetrahydroxycannabinol has antitumor activity against recurrent glioblastoma multiform in phase 2 trial in human [32]. Combination of surgery, chemotherapy and radiotherapy is the cornerstone of pediatric tumor management [33]. Dexamethasone is recommended

for symptom relief in primary high-grade glioma at a maximum dose of 16mg in 4equal doses and should be tapered rapidly where necessary. But patients with high-grade brain tumors can take maintenance dose (0.5–1.0 mg) daily. But when one of the followings endocrine, muscular, skeletal, gastrointestinal, psychiatric and haemalotogic complication is observed, the drug should be withdrawn immediately [34]. Mobile cell phone can cause glioma meningioma and acoustic neuroma [35]. Lack of specialized multidisciplinary team may make surgical intervention difficult [36]. There was more incidence of benign CNS tumors (61%) than malignant CNS tumors (39%) suggesting the need for specialized care [37]. A blunt age-related decline in basal metabolic rate (BMR) was associated with high mortality reflecting poor health status [38] indicating that young cancer patients may respond better to the cancer chemotherapy than the very elderly ones. Metabolic reporgramming in brain tumors influenced by tumor microenvironment contribute to drug resistance and tumor recurrence. However, altered metabolism may provide effective therapy for brain tumors [39]. The calculated radius (4 cm) of glioblastoma, planum sphenoidale meningioma (1.85 cm), multimeningioma (0.55 cm) secondary to pituitary adenoma (Table 2) shows that pituitary adenoma could cause secondary brain tumors in both man and woman] of 50–63 year. Pancreatic cancer of 4.5cm could lead to brain metastasis of 4cm in woman [40]. Primary brain tumors occurred in the adults within age range of 37–82 years. Females are more affected and surgical removal remains the major intervention and the prognosis is poor [41]. Side of head of interventional cardiologists/radiologists is more vulnerable to brain tumours [42]. Prognosis of congenital brain tumours is poor with the longest median survival seen in choroid plexus papilloma and astrocytoma, but teratomas are rapidly fatal [43]. However, Kernel statistical method for evaluation of continuous risk variables could be combined with Cox model that determines threshold of continuous variables for determination of survivability of patients with primary brain tumours [29]. Mathematical model of glioblastomas that incorporates tumor growth, cancer cell diffusion and cell proliferation rate is clinically useful and predictive [9]. Regardless of treatment protocol, the life expectancy of gliomas is 9–12 months [44]. The maximum tolerated dose of single fraction of radiation surgery is 15–24 y for tumor diameter (≤ 20mm – 40mm) [45]. The brain synchronizes billions of neuronal cells for physiological and psychological function. But malignancy changes the function of brain as observed in glioblastoma patients with 5% chance of 5years survival in adult and 20% chance of 5 years survival for glioma in children [46]. The patients treated of glioma could have neurological impairment leading to low intelligent quotient (IQ). The concentration of the tumor mutant alleles varied from < 5–3000 copies /ml of cerebiospinal fluid (CSF) and of somatic mutations have been identified [47]. Mobile phone radiation could cause glioma, acoustic neuroma, meningioma and brain cancer when phones are used < 1–5 years [48]. However, methyl cholanthrene could cause brain tumors [49]. However fish intake was associated with lower risk of brain cancer risk [50], despite the increased risk of glioblastoma multiforme being associated with environmental or life style factor [51]. Brain metastases are commonly associated with cancers of lung, breast and colon. The symptoms are headache, nausea and vomiting, seizures, dizziness, weakness in hands, arms, feet and legs, blurred vision, slurred speech and decreased memory or concentration [52]. Genetic disposition of brain tumor with the increased incidence from the age 30 years and low incidence of 75 years and male: female ratio of 1.5:1 show that women are more likely to develop meningiomas than men [53], suggesting that gene therapy may be a potentially beneficial to human brain tumors as opposed to aggressive surgical resection, radiation and chemotherapy. The WHO grading of CNS tumors is as follows: grade I (slow-growing tumor, postoperative healing after resection, long term survial), grade II (comparatively slow growing, progresses to malignancy, often recurs), grade III (High proliferative potential, malignant, requires adjuvant radiation/chemotherapy) and grade IV (rapidly proliferative, malignant, highly aggressive) respectively [54]. However, radiotherapy of parkinsomsm patient with brain tumor is relatively safe [55].Assessment of potential risk should be based on tissue or organ radiation dose and understanding of the corresponding dose-response relationships [56].Tissue weight is relative to radiosensitivity and assumed total risk of radiation. Hence hypothetical tissue factor is assumed to be 1.0 [57] but weighting factor for brain is 0.01 [58].

Table 2
Mathematical parameters of multiple primary brain tumors with diverse origin in human

S/N	Tumour Type	Sex	Age	Location	Dimension (cm)	TV (cm^3)	TW (g)	Density	TP	RM (cm^2/yr)	Radius (cm)	Comments
1.	Meningioma/diffuse astrocytoma	F	68	LFL	4.5x4.5	47.7	45.56	0.96	7.9 x 10^{10}	20.25	2.25	Dead
2.	Glioblastoma multiform/pituitary adenoma	M	63	RFPL	5.2x6.8x5.4	164.59	99.14	0.60	1.7 x 10^{11}	36.72	3.40	Dead
3.	Glioblastoma multiform/pituitary adenoma	M	63	SF	2.0x2.1x2.9	12.77	6.39	0.50	1.1 x 10^{10}	6.09	1.45	High survival
4.	Planum sphenoidale meningioma pituitary adenoma	F	62	PS	3.7x3.0x1.8	26.52	16.65	0.63	2.9 x 10^{10}	11.1	1.85	Dead
5.	Pituitary adenoma/multi meningiomas	F	50	SR	1.1. x 1.0	0.70	0.55	0.79	9.5 x 10^{8}	1.10	0.55	High survival

Keys: LFL = Left frontal lobe; RFPL = Right frontoparietal lobe; SR = Sellar region; PS = Planum sphenoidale; TV = Tumor volume; TW = Tumor weight; TP = Total proliferation; RM = Rate of migration

Hypoxia PET tracers could be used to identify tumors at preclinical stage [59]and manual radiotherapy may yield better result than automated radiotherapy [60]. Histological primary brain tumors are pilomyxoid astrocytoma, pleomorphic xantho-astrocytoma, subependymal giant cell astrocytoma, fibrillary astrocytoma, anaplastic astrocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, glioblastoma with oligodendroglial component, small cell glioblastoma, glioblastoma with primitive neuroectodermal tumor-like component, adenoid glioblastoma, granular cell glioblastoma, gliomatosis cerebri, oligodendroglioma, mixed oligo-astrocytoma, myxo-papillary ependymoma, sub-ependymoma, cellular ependymoma, clear cell ependymoma and tranycytic ependymoma. Others are demoplastic medulloblastoma, classic medulloblastoma, anaplastic medulloblastoma, CNS- primitive neuroectodermal tumor, atypical teratoid tumor, ganglioma, gangliocytoma, astrocytoma, dys-embryoplastic neuroectodermal tumor, central neurocytoma, extra-ventricular neurocytoma, cerebellar liponeurocytoma, papillary glio-neuronal tumor, Rossatte forming tumor of the 4th ventricle, choroid plexus papilloma, atypical choroid plexus papilloma, choroid plexus carcinoma, pineocytoma, pineal parenchymal tumor of intermediate differentiation, pineoblastoma, papillary tumor of the pineal region, angiocentric glioma, choroid glioma of the 3rd ventricle, astroblastoma, and cribriform neuroepithetial tumor [61]. Response to analgesics against pain from any of these tumors may be hermetic yohimbine, clopamine, promethazine, levodopa, prostaglandin, cannabinoids, nocistatin, histogranin, calcitomin, hyprenorphine, morphine, and antiemetics may be used [62]. But congenital brain tumors that may manifest few days after birth account for 0.5–1.9% of all paediatric brain tumors, teratoma being the most common type. Diagnosis is usually difficult, though based on clinical characteristics, radiological findings, magnetic resonance imaging and ultrasonography. The prognosis depends on histopathological features and the tumor location, hence the treatment is difficult [63]. Brain tumors are the 2nd most common cancers after haematological malignancies accounting for 21% of all childhood cancers affecting children of $\leq$ 14 years, males are more affected [64]. Cerebrospinal fluid, flow cytometry, proteomic, micro RNAs analyses could be used for discovery of brain cancers [65]. Pilocytic astrocytoma is associated with high fetal growth [66]. But prostate cancer could cause solitary brain metastasis [67] as trauma could also cause glioma [68], suggesting that benign brain tumors could significantly increase annually with part of temporal attributable to improved diagnostic imaging techniques [69].

A 2-day old male baby weighing 2.6 kg of height 0.43m and cranial circumference 0.34m was diagnosed of brain tumor [70]. Gliosarcoma is a high-grade glioma and a variant of glioblastoma multiforme. It accounts for < 2% of all glioma and 5% of all astrocytomas [71]. Early brain tumor could manifest first sign as bradycardia [72]. Meningiosarcoma (cerebral sarcoma) was treated in a 3-year-old boy by surgery and radiation and 55 years later, rebonced, suggesting that comprehensive medical history could reveal early diagnosed pediatric brain tumors [73]. Large cystic astrocytoma could be removed successfully without recurrence. The affected babies had large heads [74]. Therefore, histology, conventional molecular tests and methylation arrays could be used as diagnostic markers for adult brain tumours [75]. Gliomagenesis by traumatic brain injury could be proven by radiography [76]. Environmental risk factors for brain tumors are ionizing radiation, mobile phone, extremely low frequency electromagnetic fields, specific infections, allergies diet, tobacco, alcohol, chemical agents, occupations and head trauma or injury [53]. But metastatic brain tumors may respond to paclitaxel [77]. Metronomic (low-dose) chemotherapy is effective in children [78]. Hence, there is need to explore formulas that can be used for calculation of safer low doses of chemotherapeutics for brain cancers. Cancer chemotherapy can be classified as primary, an adjuvant and palliative [79]. The three most common brain tumors are medulloblastoma, glioma and ependymoma, but targeting specific brain tumor pathways and mutations to improve efficacy with a reduced toxicity are very important [80]. One drug fits all therapy paradigms should be replaced by individualized therapy for specific brain tumors [81]. High doses of bleomycin are effective and can be used in the treatment of craniopharyngiomas (5- 17.5 mg/kg), glioblastoma 7 mg/kg and astrocytomas 3 mg/kg with few patients exhibiting transient fever, headache, vomiting, lethargy and

peritumoral edema [3]. Small molecule kinase inhibitors could be of great benefit for the treatment of glioblastoma multiform and other brain metastases [68]. Born neutron capture therapy (BNCT) is a form of radiotherapy which combines neutron irradiation with a boron. The high linear energy transfer (LFT) is deposited in a range of 10μm, an equivalent of cell diameter [82]. Radiotherapy of glioblastoma multiform (GBM) could lead to more aggressive form of the cancer. But targeting protein (MDA – 9 or Syntenin encoded by melanoma differentiation-associated gene with a small molecule inhibitor may prevent this side effect. Also the drug against brain cancer targets a protein interaction domain in MDA-9, blocking signaling pathways that promote invasiveness and proliferation in glioblastoma cells. Tumor sensitivity to radiation and improved survival is also boosted [83]. Computed tomography-related radiation could increase the risk of brain tumors [84]. The risk factors of child brain tumors are ionizing radiation exposure, cancer syndromes, age, birth defects, and fetal growth among others [85]. Subtle symptoms such as headache are associated with aging and brain tumor [86].

Conclusion

Occult primary brain tumor is more proliferative than multiple primary tumor of brain with low prognosis. Teratoma is the most deadly followed by glioblastoma multiforme/pituitary adenoma, meningiosarcoma, and meningioma/diffuse astrocytoma, gliosarcoma, planum sphenoidale meningioma, glioblastoma multiforme/pituitary adenoma and solitary brain tumor. The tumors affect human of both sexes within the age range of 2–79 years. Brain tumors are mostly diagnosed in advance stage, when all forms of treatment will have been useless.

Declarations

Compliance with Ethical Standards

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Disclosure of potential conflicts of interest

Author SAS declares that he has no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable.

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