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Functional Issues in Brain Tumor Treatment

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Abstract

The limited success of current treatment options that attempt to shrink brain tumors, along with the accompanying compromised quality of remaining life, raise increasing concerns about the adverse effects of cancer treatment on brain function. Some aggressive cancer treatments can directly damage normal brain tissue that surrounds the tumor, while other regulatory paradigms may harm neuroplastic mechanisms which are important in functional recovery. Functional outcome is a major target in clinical trials, but seems to be neglected in translational brain tumor research. Some recent research has started to fill the critical behavioral void in this field. Optimal treatment strategies would cure the disease and save life without reducing the integrity of the brain. Furthermore, neurorehabilitative treatments are needed to repair the damage caused by not only brain tumors but also conventional cancer treatment approaches.

Keywords: Brain tumor; Behavioral measurement; Neuroplasticity; Recovery of function; Quality of life

Introduction

In 2000, it was estimated that 16,500 new cases of primary brain tumors would occur in the United States, with 13,000 deaths [1]. Although brain tumors constitute only a small proportion (about 1.4 percent) of overall human malignancies, they carry high rates of morbidity and mortality. More terrifyingly, brain tumors often strike young people. Central nervous system neoplasm is the second most common type of childhood malignancy (after leukemia) and the second leading cause of cancer deaths in children [1]. Furthermore, brain tumors are among the most devastating to patients, because they affect an irreplaceable organ that fundamentally defines each individual's uniqueness.

Brain Tumor Treatments and Their Impacts on Brain Function

Conventional brain tumor treatments include surgery, radiation therapy and chemotherapy. Surgery is generally the first step and the most effective treatment for reducing tumor size as well as brain pressure for both malignant and non-malignant brain tumors. Radiation therapy plays a central role in the management of malignant tumors. Radiation therapy plus surgery has been shown to extend the life expectancy of patients with malignant gliomas compared with surgery alone [2,3]. Chemotherapy is important in the treatment of some but not all types of brain tumors in helping to extend the survival time of patients.

Although most primary brain tumors rarely metastasize, the regional infiltration into the surrounding normal tissue during tumor progression leads to badly demarcated borders and underlies their great propensity for recurrence [4]. High-grade gliomas are the most frequent primary brain tumors in adult patients. The high incidence of recurrence and poor prognosis of malignant gliomas compel the development of more powerful anti-cancer treatments. Many treatments that can shrink brain tumors may not meaningfully increase survival, and even if they increase survival, they may not necessarily improve function, at least not optimally. The compromise of the quality of remaining life as well as the limited success of current treatment options in shrinking tumors raise increasing concerns about the adverse effects of cancer treatment on brain function. Deterioration in neurological function is accompanied by significant deterioration in the global quality of life in patients with high-grade glioma [5]. In the clinic patients, the impact of radiation and chemotherapy on the quality of life has to be considered before initiating treatment, and once treatment-related neurological or cognitive deficits occur, acute and long-term neurotoxicities need to be weighed against the benefits in order to decide whether the dose should be lowered or the therapy should be terminated [6].

The following sections discuss why aggressive brain cancer treatments are not commonly implemented, and how different treatment modalities may adversely affect brain function and harm neuroplasticity.

Surgery

Surgery is the most important treatment modality that is aimed at maximal debulking of the tumor burden. However, surgery can directly damage surrounding normal brain tissue. A particular difficulty in the treatment of brain tumors, in contrast to other types of tumors, is that every brain area is specialized for certain functions. Some tumors can be removed completely, such as meningiomas and grade I gliomas, for which, surgery is curative. In general, a surgical resection as complete as possible is recommended, as long as tumor can be removed safely without leaving an unacceptable neurological deficit. However, even when all visible tumors are removed during surgery, there are still chances of local recurrence. Tumors that are in deep parts of the brain or involve critical structures, such as those that allow one to speak and understand, however, may not be even partially resectable.

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Radiation therapy

For low-grade gliomas, radiation therapy with a total dose ≤ 50 Gy in 1.7 to 2 Gy daily fractions is usually used with the 5-year survival rate of 50% [7]. For high-grade gliomas, large, randomized clinical trials demonstrated that 60 Gy has a significant survival advantage over 50 Gy [8,3]. Thus, the standard dose for high-grade gliomas is considered to be 60 Gy in 30-33 fractions [7]. However, most patients show recurrence within 2.0cm of the pre-surgical, initial tumor margin, implicating that current radiation doses are inadequate for treatment of the primary tumor [9-11]. No survival difference was found between limited-volume radiation and whole-brain radiation, since new intracranial metastases are always antedated by tumor progression at the primary site [12]. Even with high-dose (70 or 80 Gy) conformal irradiation, the great majority of cases still failed with central or in-field recurrences, suggesting that further dose escalation to 90 Gy and beyond is reasonable [13]. Although local recurrence is still inevitable following high-dose radiation, central recurrence is delayed and the survival time is extended [14]. By general consensus, increasing the amount of radiation delivered to gliomas results in enhanced tumor cell death and a trend of improved survival.

However, the neurotoxicity limits further dose escalation. With standard external beam radiation, a dose of 60 Gy exceeds the threshold for toxicity [15,16]. The tolerance of the brain to radiation depends on the dose per fraction and the total dose applied [15]. Cranial radiation can induce some generally mild and self-limited acute complications, including increased intracranial pressure and exacerbation of preexisting neurological symptoms that are due to edema and demyelination. However, clinical studies demonstrate that chronic, potentially fatal or permanent complications can also occur and are characterized by seizure, dementia, growth failure in children and other neuropsychological impairments that are a result of direct damage to the brain and blood vessels [17-20].

Radiation therapy may harm neuro-plasticity. In animal models, low-dose radiation attenuates neurogenesis and exacerbates ischemia-induced cognitive deficits [21] and radiation-induced cognitive impairments can be detected with spatial learning tasks and are associated with a decrease in hippocampal neurogenesis [22].

Chemotherapy

Some tumors such as grade 2 and 3 gliomas require chemotherapy in addition to surgery and radiation therapy. Glioblastoma multiforme is refractory to treatment; however, chemotherapy when combined with surgery and radiation carries a small therapeutic benefit. However, chemotherapy as well as radiation is widely blamed for further neurological complications in brain tumor patients [23,20]. Children who were treated for supratentorial tumors had significantly more learning problems, and children who were treated for infratentorial tumors had significantly more behavioral and social problems [23].

5-fluorouracil is a widely used and studied chemo regimen. Systemic chemotherapy with 5-fluorouracil can lead to central neurotoxicity [24-30], although not common and typically subtle. Candidate mechanisms for chemotherapy-induced cognitive changes include DNA damage, telomere shortening, cytokine deregulation, and estrogen decline, which may act independently or interactively [31]. Genetic variability in blood-brain barrier transport of chemotherapy agents, DNA repair capacity, neural repair capacity and neurotransmitter regulation affects cognitive function in cancer patients after chemotherapy [31]. Impaired performance in several learning and memory tests was observed in mice receiving a combination of two anti-cancer drugs, methotrexate and 5FU, which may be attributed to functional changes in specific brain regions, including the frontal lobes and hippocampus [32]. Normal brain cells, especially progenitor cells and oligodendrocytes, which play important roles in neural repair, are more susceptible to chemotoxicity than cancer cells, and systemic administration of chemotherapeutic agents leads to reduced cell division and increased cell death in the adult mouse brain even long after drug exposure [33].

New compounds, that demonstrate selective tumor localization and/or can increase the sensitivity of tumor cells to radiotherapy, chemotherapy, and photodynamic therapy [34-39], represent a potential future of cancer treatment.

Novel experimental brain tumor treatments

Local chemotherapy: Local chemotherapy has been actively investigated in the latest decade. Fluorouracil (5FU) has been widely used as a local chemotherapy agent. The potential reasons are, first, 5FU is hydrophilic, and does not readily cross the blood brain barrier (BBB). When systemically administered, 5FU has very little effect on malignant gliomas and other tumors implanted in the brain [40-42]; however, it shows some effect on the same types of malignant brain tumors implanted in the flank [43,44], indicating that its lack of effectiveness is due to its limited concentration inside the tumor. A direct drug delivery of chemotherapy, such as 5FU, to the brain tumor can increase drug levels in the tumor area and can also decrease undesired systemic side effects [45-48]. Second, 5FU has relatively less direct neurotoxicity compared to other commonly used chemotherapy drugs. 5FU is an anti-metabolic drug. The mechanism of action of 5FU is associated with the incorporation of 5FU into DNA and RNA and the inhibition of nucleic acid synthesis, thus affecting actively proliferating cells [49]. A recent study in rats has shown that regional delivery of 5FU into the sensorimotor cortex can initiate functional impairment in a healthy brain, while following a focal cortical tissue displacement that is partly characteristic of a brain tumor, it can exaggerate secondary degeneration and impede functional recovery [50].

Anti-invasive and anti-angiogenic treatments

Regulatory paradigms, such as anti-invasive and anti-angiogenic treatments, are aimed at controlling tumor growth and spread [51]. The regulatory paradigms may not directly damage normal brain tissue, but they may harm the neuroplastic mechanisms which are important in functional recovery.

To a limited extent, the brain is capable of repairing itself after damage. Emerging data support the essential roles of neurogenesis, angiogenesis, upregulation of growth factors and inhibition of spontaneous apoptosis in recovery and restoration after stroke and other brain injuries [52-57]. However, many of the developmental and neuroplastic mechanisms might also be what brain tumors rely on to support growth, differentiation, invasion and metastasis and therefore targets of brain tumor treatments [58-62]. For example, gliomas are angiogenesis-dependent [63,64]. Vascular endothelial growth factor (VEGF) secreted by glioma cells plays a prime role in the induction of tumor angiogenesis [65-67]. The neutralization of endogenous VEGF suppresses the growth of gliomas [68,69]. However, inhibition of VEGF also impedes revascularization and neural repair after brain injury in a rat stab wound model [70]. Similarly, FGF-2 produced by some types of gliomas is related to angiogenesis and tumorigenicity [71-74]. Inhibition of basic fibroblast growth factor (FGF-2) impedes glioma growth [74]. However, blockading FGF-2 with neutralizing

antibodies retards functional recovery following suction lesions of the motor cortex in rats [75], because FGF-2 is one of many neurotrophic factors that can enhance recovery from brain injury [76,77]. Long-term blockage of N-methyl-D-aspartate (NMDA) glutamate receptors limits glioma growth in rats by inhibiting proliferation and migration of tumor cells as well as inducing tumor cell death [78-80]. However, after a delay, this drug can adversely reverse functional recovery in rats with compressive mass injury to the sensorimotor cortex [81], possibly because glutamatergic activity at NMDA receptors may be involved in chronically maintaining neural adaptations linked to restoration of function [82].

Can a Brain Tumor Induce Neuroplasticity?

Tumor-induced brain damage is characterized by various injury patterns, such as cerebral ischemia, mechanical compression, denervation, and excitotoxicity, all of which can trigger brain plasticity [54,83-88,57,89-91,81,92,50,93-96] that likely fosters functional recovery [53,55]. The relatively slow growth pattern of brain tumors makes the brain's responses to them likely to be similar to the gradual adaptive mechanisms observed in progressive neurodegenerative diseases [97], and prevents early diagnosis. Recent studies have shown neurogenic responses of the subventricular zone (SVZ) to malignant brain tumors grown in the striatum [98,99,100], as well as reactive peri-tumoral plasticity-related changes, including synaptogenesis, astrocyte activation and angiogenesis [101], suggesting that a brain tumor, like other lesion types, is able to elicit neuroplasticity. The peri-tumoral and/or remotely located mechanisms of brain plasticity may continuously compensate for tumor-associated insult, potentially contributing to the stealth nature of brain tumors.

Neurorehabilitative Treatments are Needed in Brain Tumor Management

Neurorehabilitative treatments may be helpful in repairing the damage caused by brain tumors themselves and the neurological impairment that is frequently associated with conventional approaches to cancer treatment. An increase in the intensity of aggressive cancer therapies may be allowed by the availability of neurorestorative regimens, which might keep the neurological side effects at a tolerable level, thus leading to maximum elimination of brain tumors along with reduced adverse impact on functional outcomes.

Current supportive treatment primarily includes anticonvulsants and corticosteroids, focusing on relieving symptoms [7]. Corticosteroids can help manage side effects such as nausea, but may impact mood and memory [102]. No neurorehabilitative strategy is clinically available to protect the brain from treatment-related toxicity while also improving long-term neurological function. A limited number of studies have aimed to investigate regimens with neurorehabilitative effects. Ramipril, an inhibitor of angiotensin-converting enzyme (ACE), was shown to ameliorate radiation-induced brain damage in a rat optic neuropathy model [103]. A thrombin inhibitor was used in a rat glioma model to reduce tumor size while also providing functional benefit [104,105]. A preliminary, retrospective investigation in a sample of patients with primary malignant brain tumors demonstrated the effectiveness of postacute brain injury rehabilitation methods, originally developed for traumatic brain injury survivors, in ameliorating neurobehavioral deficits due to the tumor, surgical resection, and subsequent radiation and chemotherapy [106].

However, in addition to the dilemma that treatment regimens targeting tumor promotion pathways may depress neuroplasticity and functional recovery, the possibility that treatments able to protect and benefit injured neuronal tissue may also protect and benefit tumor tissue creates another dilemma confronting brain tumor management. Injured brain tissue can excrete factors promoting dendritic growth and functional recovery [107]. Fluid derived from wound injury was shown to accelerate growth of C6 glioma in spheroid culture, suggesting the stimulatory effect of injury on tumor progression [108]. Therefore, as a premise of any applicable value, the effects of neurorehabilitative treatments on tumor growth and regrowth should be cautiously investigated.

Can Brain Repair and Tumor Suppression Possibly be Monitored in the Same Way?

Brain repair and tumor suppression may not always be contradictory and can possibly be monitored in the same way. Malignant glioma cells attract endogenous precursor cells as a reparative mechanism and the presence of precursor cells is antitumorigenic [98-100]. Increased neuronal differentiation and synaptogenesis are associated with decreased aggressiveness in retinoblastoma [109]. Neurotrophins [Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and Neurotrophin 3 (NT-3)] are pivotal mediators of proliferation, differentiation, and survival of cells in the normal brain [110]. BDNF is widely established as a major trophic factor in the functioning of both normal and injured brains [55,111-114]. Human origin gliomas generate neurotrophins with BDNF being the most abundantly expressed, and extrinsic neurotrophins fail to stimulate mitosis of the glioma cultures [115]. There is evidence that neurotrophin signaling is involved in the process of apoptosis and neuronal differentiation in medulloblastomas [116,59]. Whereas in normal blood vessel angiopoietin (Ang) -1 expression exceeds Ang-2 expression, the opposite is true in tumor blood vessels [117,118]. Blocking the stabilizing effect of Ang-1 on both preexisting and newly formed blood vessels by Ang-2 cooperates with VEGF to induce tumor blood vessel growth [119-122,117,118,123]. Therefore, normalization of the expression pattern of Ang-1, Ang-2 and their endothelial cell receptor Tie2 may normalize the abnormal structure and function of tumor vasculature to make it more efficient for oxygen and anti-cancer drug delivery [124]. Interestingly, in addition to reducing vascular permeability and enhancing vascular stabilization and maturation [125,126], Ang-1 can trigger the migration of immature neurons to the site of brain damage and promote functional recovery after stroke [127], thus linking the two processes of neurogenesis and angiogenesis together.

Functional Assessment is Important in Translational Brain Tumor Research

The main challenge facing modern brain cancer research is to develop novel interventions or improve existing treatments, to reduce undesirable neurological side effects while maintaining anti-cancer efficacy, as well as to design therapeutic regimens that can provide neuroprotection during cancer treatment or promote neurorestoration afterwards. In clinical trials, functional outcome is a major target, but seems to be neglected in translational brain tumor research. This might be accounted for by the assumption that the primary goal of a cancer treatment is to prolong life, and that reduction of tumor size may consequentially lead to functional improvement. Furthermore, it may also be the lack of suitable experimental approaches to assess functional outcomes, which, unfortunately, has placed a serious limitation on the ability to weigh the risks and benefits of new cancer therapies and to develop strategies to rehabilitate damaged functions.

Recent Research Progress in Behavioral Neuro-oncological Field

Before functional assessment can be included in evaluating the efficacy of potential treatments, simple methods for measuring behavioral changes in animal tumor models should be established. Brain tumors growing into different locations cause different neurological deficits, and accordingly, require different behavioral testing methods in animal models. The staircase test, which is an assay to determine skilled paw-reaching ability, has been used to measure progressive focal neurological dysfunction following experimental implantation glioma into the striatum in rats [129]. A recent study showed significant average sensorimotor deficits in rats bearing 9L glioma implanted into the sensorimotor cortex, but only when tumor growth was extensive [101]. A case-by-case analysis of brain tumor volumes measured by magnetic resonance imaging (MRI) and corresponding behavioral performance revealed a significant correlation between tumor volume and magnitude of somatosensory asymmetry, indicating that the somatosensory asymmetry test is a useful tool for gauging the extent of tumor progression [101].

In the investigation of functional outcome after a novel antiangiogenesis regimen in nude mice implanted with U87 glioma into the sensorimotor cortex, the combination of antibodies against both VEGF receptor -1 and 2 reduced glioma growth and delayed the onset of significant sensorimotor deficits in tumor-harboring animals [129]. A reduction in tumor size may result in functional improvement in parallel, however, the effects of tumor reduction may mask the adverse effects of the treatment on the integrity of brain function.

A model that can hold tumor size constant independent of treatment may help more directly assess the potential detrimental effects of tumor growth inhibitors on brain plasticity. A technique of epidural implantation of a hemisphere-shaped plastic bead overlying the sensorimotor cortex has been used to isolate the compression characteristics of a brain tumor [130,131,92]. Rapid brain compression induced mild sensorimotor deficits shown in forelimb-use asymmetry test (cylinder test), somatosensory asymmetry test, foot-fault test, tapered ledged beam test, and vibrissae-evoked forelimb placing test, which depended on the location, magnitude and duration of the focal compression [92]. This model was then applied to examine the impact of some cancer interventions on the compressed brain. Long-term administration of the NMDA receptor antagonist MK801 did not change the recovery rate but caused a reinstatement of behavioral deficits after complete recovery from focal brain compression [81]. Local chemotherapy with 5FU exacerbated compression-induced functional deficits [50]. The mild lesion pattern and the resultant neuroplasticity in this mass compression model make it especially suitable for detecting the adverse effects of anti-cancer treatments on functional integrity of the brain. Taken together, use of both a tumor implantation model and a controlled-rate non-tumor compression/decompression model may prove very useful in the investigation of optimal treatments.

Perspectives

A further investigation to develop a controlled-rate focal compression model is warranted for testing anti-cancer drugs that possess tumor-shrinking effects and thereby determining which drugs operate efficaciously along with reduced harm to the compressed brain and its plastic ability.

To show "proof of principle", the same anti-cancer therapy, administered at the same dosage, by the same route, and under the same schedule, in both the non-tumor compression model and the tumor implantation model, is needed to bridge these two treatment screening systems. An example of an anti-cancer treatment that can interfere with functional recovery in the non-tumor compression model but can slow tumor growth and concurrently delay the onset of significant functional deficits in the tumor implantation model, may better demonstrate the necessity of utilizing both models to screen for treatments that have both improved anti-cancer effects and reduced adverse effects on functional integrity of the brain.

Because the hippocampus may be affected both by the tumor and by certain anti-cancer treatments, the water maze test and other tests for cognitive function are necessary for the measurement of functional outcome [132].

It would be interesting to block some neuroplastic events, for examples, by injecting anti-VEGF, anti-BFGF, or by blocking their receptors, and then compare the behavioral responses of animals bearing tumors of similar size and location with or without treatment. This experiment would be aimed at investigating whether tumor-induced neuroplastic mechanisms contribute to behavioral compensation. Because the treatments that block neuroplasticity may also slow tumor growth, MRI would be needed to monitor tumor size and location, and the comparison should be made between treated and non-treated tumors of similar size while not considering tumor growth time.

It would also be intriguing to investigate whether behavioral lifestyles, for example, exercise, can affect glioma growth. Exercise can reduce the risk of breast cancer [133-135], significantly improve the quality of life outcome and physiological capacity of breast cancer survivors [134], prolong their survival [136], and is likely to prevent the recurrence of breast cancer [137]. Running alone or combined with caffeine guards against skin cancer in mice [138,139]. Also, motor enrichment and exercise have been shown to promote neuroplasticity and to rescue brain tissue from progressive degeneration in animal models of Parkinson's, Alzheimer's and other brain diseases [113,140].

Another important future research direction is to establish a brain injury model caused by cancer therapy with long-lasting behavioral deficits, and to examine whether neurorestorative strategies can promote functional recovery after treatment-induced brain damage. Such models may include aspiration lesion or stab wound lesions, designed to mimic as closely as possible certain aspects of tumor resection surgery and focal delivery of radiation to the normal brain. Neurorestorative strategies may include physical therapy, gene therapy, cell therapy, and neurorestorative agents such as erythropoietin, atorvastatin, and sildenafil [141-161]. Functional promotion effects should be established initially in the nontumor animal undergoing cancer therapies. The effects of the neurorestorative strategies on tumor growth and regrowth should be examined in the tumor-bearing animal with and without cancer therapies. Additional studies should explore potential integrative effects of combinations of cancer therapy and neurorestorative therapy in glioma-bearing animals. Functional outcome and survival time both should be included as outcome measures.

In summary, some recent research has started to fill the critical behavioral void in the early phases of translational brain tumor research. Longer term goals are to continue to develop models to facilitate functional assessment, to screen for optimal cancer treatment

strategies with reduced harm to brain function, and to search for novel neurorestorative strategies to promote functional outcome following standard brain tumor treatments. An improved collaboration among scientists in the areas of behavioral neuroscience, experimental and clinical neuro-oncology, neurosurgery and neurology would be needed to find better ways to help patients attain maximum functional capacity and the highest possible quality of life.

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