Original Article [CNSJ]

Brain Tumors in Elderly

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ABSTRACT

Brain tumors in elderly are increasing as the number of people, who comprise the older population, does. About half of the patients with brain tumors appear to be over 60 years of age. In this review article, Glioblastoma multiform, as the most common malignant tumor of the central nervous system (CNS) in elderly, is discussed in details of definition, prognosis, diagnosis, treatment and differential diagnosis. Other tumors such as meningioma, pituitary adenoma, the CNS lymphoma and metastasis are also included to be reviewed. Treatment plans, either conservative or aggressive, classic or novel, approved or under investigation, are presented. Furthermore different attitudes of treatment in the past and recently are also argued. Conventional therapy, surgery, radiotherapy, chemotherapy radioimmunotherapy, hormonal therapy and some other novel methods of treatments are discussed in details for the glioma. Determining factors which may be associated to the patient's response to each treatment plan are also discussed. Finally, some age related issues are provided to be paid attention to consider an old patient with brain tumor, and planning an optimal treatment in order to make the best management decisions. Until recently, people with brain tumors in elderly, were used to be treated in conservative plans and often were excluded of the clinical trials but now the number of patients who desire and receive more aggressive therapy for brain tumors is increasing.

Keywords: Brain Tumor; Elderly; Glioblastoma; Treatment

ICNSJ 2015; 2 (2):55-65 www.journals.sbmu.ac.ir/neuroscience

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Received: 1, March, 2015 **Accepted:** 18, July, 2015

INTRODUCTION

Brain tumors, either primary or metastatic, are considered as one of the major causes of significant morbidity and mortality in the elderly. The National Cancer Institute statistics, has reported an increase in overall incidence of cancers by more than 10% in the past 20 years, with an average annual percentage change of approximately 1-2% [1-3]. As well for brain tumors with the highest increase noted belonging to the population aged over 60 years old [1]. The epidemiologic factors are not well defined and the incidence of those genetically transmitted diseases associated with brain tumors, such as neurofibromatosis and the familial cancer syndromes (e.g., Li-Fraumeni), did not really show a significant increased rate [4,5]. No environmental factors such as pesticides, electromagnetic fields, or radiation exposure, have been effective in increasing the rate of brain tumors. Although there is a higher risk for meningioma in patients who had previously received head radiation therapy (RT) [1,6,7].

However, recently, the controversy has been argued whether the incidence began to raise, markedly prior to the introduction of computed tomography (CT) scans in 1973, followed by the magnetic resonance imaging (MRI), allowing to make earlier and more accurate

diagnosis [2,8-12]. In one interesting approach, records of 356 patients diagnosed during 1985 to 1987, were reevaluated by a neurologist blinded to CT, MRI, biopsy or surgical reports, as primary brain tumor with a sensitivity and specificity of 50.5% and 90.1% respectively [13].

The most common primary tumors in the elderly is glioblastoma, particularly glioblastoma multiform (GBM) with a peak on 65 years old [14]. It is classified according to the cell type as astrocytic tumors, oligodendroglial tumors, and mixed gliomas. Meningiomas are also more common in older patients with a median age of 59 and a predominancy in female [1]. Pituitary adenomas are also more common in the older population. Asymptomatic microadenomas, for example, are usually found on scans of the brain done for other reasons, e.g., head trauma, headaches, dizziness, galactorrhea, or the physical changes of acromegaly. Acoustic neuromas are benign tumors also seen in older patients, who are suspected with a unilateral hearing loss or vertigo that does not resolve with medical treatment.

Until recently, the preference of treatment for old patients was supportive care only and they were not considered appropriate to participate in clinical trials. But now, regarding the advances in discovering the molecular biology of brain tumors and their genetics in elderly. The attitude of the medical community is changing toward offering more aggressive treatments to old patients with malignancies, and some have resulted in more effective or at least tolerable in this age group. However, the overall prognosis is still poor. For this reason further studies, looking for more effective therapies, are ongoing. Age of the patient, the severity of symptoms, and the size of the tumor, histologic type and the location in the cranial cavity, neurologic compromise, patient's performance status measured by Karnofsky performance score, neurologic status, and life expectancy, defined by the neurologic deficits and coexisting medical problems, are depending factors, on which, management is decided to be either conservative (with symptomatic treatment and follow-up with serial scans) or more definitive (with surgery or stereotactic radiosurgery) [15-22].

Challenging considerations of brain tumors in elderly are the appropriate treatment, regards goals of having the tumor's growth in control and improving patient's quality of life and performance status. Each plan should be individualized to the patient, considering age as the most important but not the only influencing factor. Life expectancy according to the performance status and coexisting chronic illnesses should be kept in mind. A patient with good performance status or small sized tumors and an acceptable histologic features, would be managed by more aggressive treatments and resections. While patients with poor performance status and significant neurologic deficits, multifocal tumors, and debilitating medical problems would be limited to corticosteroids and supportive care. An optional addition of palliative RT, desired by the patient, might be considered. The patient and the family should be taken into the discussion of planning the optimal cost beneficial treatment in manner of neither discourage therapy nor raise false hope. Therapy can prolong survival with reasonably good quality of life. All the options should be discussed in all aspects and they should be involved helping the treating physician making the right choice [1,23-25].

Diagnosis

The diagnostic factors of brain tumors make a triad of clinical presentation, imaging studies, and histology [26]. In the older population "a short period of time" in the onset of symptoms (e.g., less than 6 month) can be an alarm of a malignancy rather than the normal aging signs. Gait disturbances, short-term memory deficits, localized and persistent headaches and seizures are the most common symptoms at presentation. As the tumor grows and exerts pressure, symptoms get worse. The degree of neurologic compromise is an important factor in planning the therapeutic approach. However tumors of the anterior frontal lobes, the anterior temporal lobes, which are the most common ones, or those at the base of the skull can grow to a large size, presenting few or no symptoms or with nonspecific symptoms often mistaken to the aging process (e.g., memory loss, personality changes, or some gait difficulties).

Unilateral hearing loss, vertigo, and mild face weakness are symptoms caused by acoustic neuromas which are distinguished from vertebrobasilar insufficiency, by imaging studies. To date, MRI scans in axial, coronal or sagittal planes, are known as the modality of choice in studying the tumor in three-dimensional view, visualizing its surrounding structures and very small lesions, especially those in temporal tip, in the inferior frontal lobe or posterior fossa, and at the base of the skull, with a higher resolution contrast than CT. Gadolinium-diethylenetriamine pentaacetic acid is used to differentiate neoplasms from other intracranial lesions, and to identify even subtle changes in the appearance of a tumor during treatment [27]. It can also be useful in diagnosing leptomeningeal metastases, which are seen more and more as brain tumor patients survive longer. Positron emission tomography (PET) scans and single

positron emission computed tomography (SPECT) scans can help to distinguish tumor necrosis from radiation-induced necrosis in the follow-up of tumors after therapy. MR spectroscopy is still a research tool but might turn into the noninvasive diagnostic modality choice in differentiating low-grade from anaplastic gliomas.

Glioma

GBM is the most aggressive and most common primary brain tumor, classified according to the cell type as astrocytic tumors, oligodendroglial tumors, or mixed gliomas. Common features which modify the grade of malignancy are cellularity, presence of mitoses, vascular endothelial proliferation, and necrosis. It is necessary to let the pathologist know if the patient has received radiotherapy (RT) and chemotherapy, which can cause tissue necrosis as well as some malignant tumors, particularly GBM. As a matter of fact, Gliomas which occur before age 10 and after 45, show a shorter postoperative survival since tending to be more undifferentiated and more aggressive [28].

In addition to age, it is believed that histologic features of malignancy such as nuclear atypia, mitosis, necrosis and vascular endothelial proliferation of the tumor, size, KPS score, MGMT promoter methylation status, the extent of infiltration and extent of resection [29-37] may dramatically determine prognosis and the length of post-operative survival rate. The survival advantage is particularly significant for anaplastic astrocytomas. As the 5-year survival rates were 50% in patients with astrocytomas who had a total resection but only 20% in patients who had a biopsy [38]. For patients with unresectable lesions or with associated significant medical problems, a stereotactic biopsy for tissue diagnosis seems to be sufficient. The most important prognostic factor remains the extent of resection. The postoperative residual tumor volume (determined on enhanced CT or MRI scans) correlates inversely with survival [39-41].

In many centers, elderly patients are preferred to be treated by less aggressive plans, e.g. RT alone, rather than receiving the conventional treatment due to the consideration of their reduced tolerance of treatment schedules and more possibilities of undergoing side effects, compared to younger patients.

Conventional therapy

For gliomas, the conventional therapy involves surgery, RT, and chemotherapy [17-22]. A randomized study by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) demonstrated that the addition of temozolomide (TMZ) to RT, followed by 6 monthly cycles of TMZ, significantly improved overall survival in patients with diagnosed GBM [42,43]. This protocol of treatment is currently regarded as the conventional treatment for GBM patients. However Elderly patients were dismissed by most series of investigations. Other studies have reported acceptable survival rates for elderly patients with GBM who received RT and TMZ chemotherapy with exclusion of patients older than 70 years old. The other studies concluded that adjuvant treatment including RT and TMZ chemotherapy was tolerable for elderly patients of GBM [44]. As a result, elderly patients are not deserved to be deprived of conservative treatments. As they showed more survival gain than the younger group when receiving conventional treatment, and the presence of complications such as pneumonia and bone marrow suppression were neither significantly different in rate nor affect the difference in survival.

Surgery in glioma

Surgery is the first therapeutic intervention for brain tumors, with the goal of tissue diagnosis and, whether possible, complete resection and debulking the tumor to reduce the pressure. In addition surgery causes rapid clinical performance improvements and a significant increase in survival rate by providing a chance of better response to subsequence plans by the cytoreduction mechanism. In elderly, gliomas, even with a low grade histology tend to behave more aggressive. Therefore surgery, RT and chemotherapy are the treatments of choice. Perfected treatment modalities are developing. Surgery, for instance, to perform a biopsy (open, stereotactic or frameless stereotactic), or resection technique in form of computer assisted craniotomy, which is minimally invasive and more acceptable in older patients with resectable tumors.

Reoperation for recurrent or progressing tumors would be considered variable case by case, depending on the tumor type, expected survival, KPS, patient's age, and plans for further therapy [39,45,46]. Age was presented as an influencing factor to the outcome. One study, showed a 57 weeks of survival for patients younger than 40 but only 36 weeks for older ones [47]. Other studies also found a correlation between age and overall survival from diagnosis but no difference after reoperation[39]. Still the most determining prognostic factor in the survival remains the extent of resection. The postoperative residual tumor volume, determined on enhanced CT or

MRI scans, correlates inversely with survival [41,46].

The 5-year survival rates are 50% in patients with total resection of astrocytomas but only 20% in patients who had a biopsy only [38]. Patients with unresectable lesions or with associated significant medical problems could be managed in a stereotactic biopsy plan for tissue diagnosis, which seems to be sufficient.

Post-Operative Risk Factors

Since the number of elderly patients undergoing surgery for brain tumors seem to be increasing, it is important to ready for the occurrence of postoperative systemic complications and take early preventive measures. Several studies dealing with the risk factors for postoperative mortality, morbidity, and prognosis shown that the postoperative systemic complications are common in elderly patients and patients with a low preoperative KPS score [40,48-54]. Preoperative KPS score, intraoperative blood loss, and difference between pre- and postoperative hemoglobin levels were described as significant risk factors for postoperative systemic complications.

Radiotherapy

For malignant brain tumors, RT at doses of 50-60 is the standard treatment. For malignant gliomas, it increases survival compared with surgery alone. RT is also considered in low-grade gliomas in elderly. Age is still an important prognostic factor in this setting. In one study, the survival rate at 18 months for patients younger than 40 years old was 64% while it was only 8% in patients older than age 60 [55-57]. The survival rate at 18 months for patients with an initial KPS of 70 or above is 34% in comparison with 13% for patients with a KPS score of 60 or below [58]. The area that is supposed to receive RT is modified by CT or MRI scan plus considering a 3cm margin. The conventional fraction is delivered over a span of 30-33 days in daily fractions of 1.6-2.0 Gy day and the hyperfraction of 1.2 -1.6 Gy b.i.d, 1.0 Gy t.i.d. However, conventional fractionation RT have failed to provide a cure or at least long-term survival due to tumor cell resistance (particularly in hypoxic areas of the tumor), the presence of repair mechanisms, and the pattern of spread of these tumors along white matter tracts outside the radiation field [59]. But studies are still in progress to enhance radiosensitivity and delivering higher doses, shorter periods of time and safer to the normal brain tissue and therefore reducing the morbidity related rates. Cisplatin, carboplatin or BUdR are used as radiosensitizers to improve the poor performance status (KPSof 60 or below) [60-62]. Some studies have investigated the radiosensitizing effect of some chemotherapeutic agents including hydroxyurea, vincristine, and BCNU (carmustine). RSR13, an allosteric modifier of hemoglobin, is a novel radiosensitizer that binds covalently to hemoglobin which reduces oxygen binding affinity and increases oxygen release into the capillaries. RSR13 is now undergoing clinical trials. The difference in survival compared with conventional RT is not significant but apparently patients under the age of 60 seem to benefit most [63].

Side Effects of Radiation Therapy

During RT or soon after treatment some acute side effects may present, others may occur early delayed, 3 month after of RT is complete or late delayed [64].

Cognitive impairment, mostly common in temporal lobe and with baseline mild dementia, is sever particularly in elderly. Some patients complain of fatigue and headache caused by edema, or their neurologic deficits sometimes get worse. Depending on the Tumors location, nausea, sore throat, hearing loss, or blurred vision may happen. They are often transient and corticosteroids and reassurance would help. Early delayed symptoms present as somnolence, loss of appetite, and apathy which are self-limiting but much more severe in older patients. And late-delayed symptoms includes short-term memory loss and cognitive decline [65]. CT or MRI scans show white matter changes bilaterally or enhanced areas of focal radiation necrosis surrounding with edema [66]. PET and SPECT scans will help distinguish radiation necrosis of recurrent tumors with an increased metabolic activity pattern, while necrosis is markedly hypoactive in metabolic cycles. Biopsy makes the definite diagnosis.

Chemotherapy

Chemotherapy is used traditionally after completion of RT as adjuvant treatment or at the time of tumor recurrence or progression. Although elderly with brain tumors are often excluded from the clinical trials of new drugs and the drug combinations, combination of chemotherapy to RT is already accepted as a treatment for primary brain tumors to improve survival about 6-18 months. Depending on the grade of the tumor, could help to prolong survival by another 6-18 months. But in gliomas there are heterogeneous nature features factors including expression of multidrug resistance gene (MDR-1) and repair enzymes, which counteract the cytotoxic effect of platinum compounds and nitrosoureas. Some of the tumor cells are in the G0 phase and are less

susceptible to chemotherapy [67]. The DNA mismatch repair deficiency has been identified as an important mechanism conferring resistance to RT and methylating agents such as procarbazine and temozolomide [68]. Nonionized and nonliposoluble drugs are limited by the blood-brain barrier [69]. Resistance to BCNU is determined by the activity of the enzyme O6-alkylguanyl alkyl transferase which is not age dependent [67]. In low-grade oligodendrogliomas, chemotherapy with PCV reduced tumor growth and induce regression of the tumor on imaging studies. Temozolomide (Temodal), has been recently approved by the Food and Drug Administration for the treatment of recurrent anaplastic gliomas. It is administered orally and is well tolerated with no significant myelotoxicity effect with no age related dose efficacy and seems to be safely administered to elderly patients [70]. Some clinical trials used chemotherapy in conjunction with RT and some recent reports suggest a benefit in using chemotherapy prior to RT, particularly in oligodendrogliomas. It seems pre-radiation chemotherapy is wisely considered for palliation in patients with old ages and low performance status 71.

The most common side effect of chemotherapy is myelosuppression, occurring in early courses of the treatment of elderly and might require blood transfusions or the use of colony-stimulating factors. No significant nitrosourea-induced pulmonary toxicity was noted in patients over the age of 60, most probably because their survival rates are low, and pulmonary fibrosis occurs after several courses of treatment. Other common side effects of chemotherapy are nausea, fatigue, and loss of appetite. These side effects are usually mild, self-limiting and responding to symptomatic treatment.

Radiosurgery

Radiosurgery including linear accelerator, gamma knife, particle beam and conformal, which was followed by Stereotactic Radiosurgery**,** was introduced as a noninvasive technique that delivers high-dose single fractions of radiation to small, well-circumscribed tumors. The treatment is safe and effective, it is done in one single dose or a few fractionated doses in an outpatient setting. For these reasons stereotactic radiosurgery is considered as a safe, effective, cost beneficial and convenient tools for the patient. The morbidity associated with this approach is primarily due to the raised peritumoral edema, which could be easily managed by corticosteroids. As gliomas mimic an infiltrative pattern of growth, it cannot afford to be the sole radiation modality. Radiosurgery can also be administered in fractionated doses.

Brachytherapy

In interstitial RT (brachytherapy) radiation sources are placed in the surgical cavity, directly into the tumor mass or adjacent to tumors with a most commonly use of 192Ir and 125I isotopes. Being more invasive than stereotactic radiosurgery and causing greater morbidity, brachytherapy in malignant gliomas can be used for infiltrating cavitary tumors, salvage therapy at recurrence, and those are larger than 3 cm. Some of considerable complications after brachytherapy are wound infections, cerebral edema, abscess into the tumor, hemorrhage, and radiation necrosis which may requires surgical intervention and make it less desirable for elderly with poor performance.

Radioimmunotherapy

Radioimmunotherapy is another method which binds to receptors expressed only by tumor and not by normal cells. It is provided by an ensured dose localization where a monoclonal antibody coupled with a radionuclide is introduced into the tumor letting the normal tissue remain safe [72].

Boron Neutron Capture Therapy (BNCT)

BNCT is a form of RT presently under investigation for treatment of malignant gliomas. It is mediated by short-range (less than 10 microns). Best result. The studies do not mention any difference in response based on tumor types, age, and performance status. The initial clinical trials have been marred by significant brain necrosis. However the improved technologies have rekindled the interest in this treatment modality[73].

Hormonal Therapy

Protein kinase C (PKC), an important factor in promoting proliferation of malignant gliomas could be inhibited by usage of Tamoxifen, an estrogen-receptor blocking agent, with a much higher dose that is proposed in treating breast cancer, particularly in malignant astrocytomas. The effect appears to be dose dependent and is cytostatic rather than cytotoxic. Still, in patients with good performance status, Tamoxifen has been shown to increase survival. It crosses the blood brain barrier and is well tolerated even at these high doses. Tamoxifen is considered to be in combination with BCNU as adjuvant therapy after RT, especially for elderly patients with malignant gliomas who had received RT and do not wish to take chemotherapy and would prefer to get other forms of treatment [74]. Thromboembolic complication was seen in a higher rate in the brain tumor

patients than in breast cancer patients, but these patients have an overall higher incidence of thromboembolism, even without Tamoxifen [75].

Novel Therapies

In Gene Therapy viral vectors are used to insert a favorable, e.g., defined tumor suppressor gene, into a targeted host cell genome. Both retroviruses and adenoviruses are used as vectors for gene therapy. The most publicized gene therapy clinical trial for brain tumors involves transfer of the herpes simplex virus thymidine kinase (HStk) gene into tumor cells, using retroviral vectors [76].

Biological therapies are discussed to be used alternates to conventional therapies, with or without RT or chemotherapies. They aim to the cell's replication factors. For angiogenesis, malignant gliomas utilize mevalonate for synthesis of cholesterol that participates in cell replication [77].

Retinoids are natural and synthetic derivatives of vitamin A, which recently have shown proven efficacy in some premalignant and malignant conditions especially on glioma cells.

These novel therapies are still in the experimental phase and need to be more investigated on evaluation of efficacy and safety in all age groups.

Manangioma

The asymptomatic meningiomas in two thirds of the patients with may not show significant growth in their clinical courses for several years. On the other hand, only about 10% of patients that were initially asymptomatic became symptomatic, in 6 months to 2 years. In elderly, is necessary to plan a careful clinical observation with repeated imaging. Study findings mentioned below will help to predict the tumor growth potential. Factors on which growth depends on, are calcification of the tumor and hypointensity caused by fibrous and hard component on T2 weighted images which may indicate to low proliferation potential, while the initial size over 30mm warns a greater potency to grow [78].

Pituitary Adenoma

Pituitary adenomas are increasingly recognized in the elderly, needing more optimal diagnosis and management plans. The clinical presentation is modified by the age related endocrine changes and related diseases. About 80% of pituitary adenomas in this age group are non-secreting, so requires to be distinguished from non-adenomatous sellar lesions [79]. Recognized secreting tumors are mainly growth hormone secreting and mostly intrasellar. Prolactinoma, which present clinically non-secreting and usually invasive and eventually Cushing's disease may appears so rarely.

Peculiar patterns of bioclinical endocrine changes in the elderly have of primary priority to be paid attention when considering endocrine parameters. They include fibrosis, vascular alternations, abnormalities in pituitary function and morphologic changes the anterior pituitary gland and subsequently, progressive growth hormone (GH) deficiency, post-menopausal changes in women, age-related androgen decline and the more recently characterized age-related changes in adrenal secretion.

In addition, due to frequent comorbid issues, a number of drug-induced hormonal abnormalities should be held in mind in this age group. Basal prolactin is adapted according to patient's age and medical conditions. Huge tumors can lead to very high prolactin concentrations, which may give rise to erroneously low values in two-site 'sandwich' assays (the so-called hook effect). GH deficiency in the elderly is hard to distinguish from somatopause, the age-related decrease in spontaneous GH secretion (the so-called somatopause). Combined stimulation with GH-releasing hormone plus arginine is a safe and reliable test to evaluate the GH secretory capacity in the elderly.

About 20% of men above 60 years have low plasma androgen levels, and an inconstant increases in LH levels. In patients with pituitary tumors, normal or decreased gonadotropins does not rule out Hypogonadotropic hypogonadism while most gonadotroph adenomas are associated with low plasma androgens, regardless of gonadotropin levels. To evaluate Hypothyroidism**,** decrease in plasma free T4 is still the best marker of central hypothyroidism in the presence of inadequately low to normal thyroid-stimulating hormone values [80].

CNS Lymphoma

Primary CNS lymphoma (PCNSL) is an uncommon form of extranodal non-Hodgkin's lymphoma (NHL), which occurs in both immunocompromised and immunocompetent hosts. In patients, who are not immunocompromised, primary CNS lymphoma shows off in elderly and needs a different management from that of other kinds of extranodal NHLs. If possible, corticosteroids should be avoided. Stereotactic biopsy should be done as soon as possible, before involving brain, CSF and eyes. Despite other tumors, resection come with no benefit in PCNSL unless the rare conditions of neurologic deterioration due to brain hernia. Whole-

brain radiation therapy alone is associated with a high risk of neurotoxicity in patients older than age 60, thus it is combined to systemic and intrathecal chemotherapy. Clinical studies show that elderly patients tolerate intensive chemotherapy well. However, with an average survival of only 1 year, the prognosis appears to be still poor [81,82].

Management of Brain Metastases

The treatment modalities for metastatic brain tumors are similar to primary ones, in addition to considering the appropriate choice of treatment, based on the condition of the systemic disease. If possible, surgical resection will significantly improve the performance status and prolong survival. Radiosurgery is an optimal choice for tumor lesions. Chemotherapy controls brain and active systemic metastatic disease, as well [83].

Differential Diagnosis

In older patients with the clinical presentation of neurologic symptoms, it is important to consider cerebrovascular diseases as an important differential diagnosis. Neuroimaging studies can be helpful when the lesion does not present a normal vascular distribution. They also help to distinguish between hemorrhage due to hypertension and hemorrhage with underlying tumor. Differentiating between primary tumors and metastatic ones is necessary when the scan reveals enhancing lesions. With a normal chest radiograph, a biopsy of one of the lesions for tissue diagnosis would be the most yielding procedure. Infectious or vasculitic lesions are less common in this age group. Skull radiographs can reveal abnormalities of the sella turcica, suggesting a pituitary tumor or erosion of the bone as seen in patients with meningiomas, as well as calcifications in low-grade astrocytomas, oligodendrogliomas, or meningiomas. Cerebral angiograms help to distinguish tumors from vascular malformations or aneurysms, and they also define the blood supply of the tumor, thus useful in surgical management [84].

DISCUSSION

Primary brain tumors in elderly often present the nonspecific features. Because of normal physiologic and cognitive changes by normal aging, thus they are often missed or delayed in diagnosis. As mentioned before, duration of the onset of symptoms is the key to evaluate primary malignancies (less than 6 month) and should be confirmed by following MRI and CT scan workup. Despite the fact that patients 65 years of age and older apparently make 44% of patients with brain tumors, only 19%, are enrolled in clinical trials and most clinical studies exclude patients over the age of 70 due to the stringent age and general health eligibility criteria, and the misconception that elderly patients would not benefit from clinical trials.

There are no therapies designed specifically for old patients with tumors. Even though molecular biology studies claim that clinical course and the tumor response to therapy in elderly is impressed by some kinds of specific age-related genetic alterations. Rate and duration of response to chemotherapy is also highly related to age, particularly over and before 60 years. Many elderly patients have to take several drugs for their chronic illnesses, thus special attention must be given to potential drug interactions of chemotherapeutic agents, especially with antihypertensive and antidepressant drugs. Reactive depression due to the brain tumors which seems to be more severe in elderly patients and needs to be treated with antidepressant medications considering patient's medical history and future plans of chemotherapy and drug combinations. Furthermore, decreased creatinine clearance needs to be considered when calculating the dose of the chemotherapeutic drugs. The aim of therapy in brain tumors with poor prognosis in elderly is improvement of quality of life, the patient's performance status, the patient's ability to perform activities of daily living and minimizing the side effects of tumor treatments. Physical and occupational therapy and an active involvement of patient's family will be helpful during rehabilitation process.

Unfortunately, there is no accurate sequence of definition to the term 'elderly'. Some studies define it as the age over 60, some others 65 or even over 70. It has been accepted that brain tumors, particularly in elderly is increasing, as the more population are compromised. To date resection of the tumor and managing the residual cells is the key to survive the patient. However, old patient were used to be deprived of aggressive approaches such as surgery. Now, the former techniques are getting more perfected and new computer assisted and minimally invasive ones seem to benefit the old age patients. New drugs are developing, adapted to the unique structure of the brain, blood brain barrier and the infiltrative and heterogeneous nature of malignant tumors. Although identifying the genes responsible for oncogenesis and drug resistance are developing significantly, finding effective treatments, particularly for malignant gliomas in elderly, has been less successful. Some studies are combining conventional therapies with novel approaches.

On the other hand, others introduce new experimental treatments.

CONCLUSION

Brain tumors in elderly, particular GBM, have a poor prognosis despite aggressive multimodality managements. In many studies, age has played significantly a negative role on prognosis. Except for low grade meningiomas, treatment is not curative and responsive in managing the tumor. Basic treatment are improved more, and molecular biology and behavioral data in malignancies are helpful to develop new novel treatments. Therefore it seems the old patients also can benefit from an individualized plan, according to their life expectations, performance, tumor stage and prognosis. Limited surgeries, radiosurgeries, chemotherapy with controlled toxicity are some instances of improved access and acceptance of invasive plans for brain tumors in elderly. Brain tumor in elderly needs to be studied more and further investigations and clinical trials are demanded, which specific design for elderly.

ACKNOWLEDGEMENTS

The Authors deeply thank Mr. Esmail Seddighi and Mrs. BanooAshraf Saberi for their great contribution in data gathering and editing the manuscript.

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