Review Article

A Review of Conservative and Latest Techniques of Treatment of Glioma

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Abstract

Glioma is the most common primary intracranial tumor. Many modes of treatment are used for treating glioma, among which some are conservative while some are emerging as latest modes of treatment. In this article, we reviewed some of these methods and assessed the practicality and effectiveness of their approach. We came to a conclusion that both conservative and latest techniques are proven successful as far as the outcome is considered. However, latest modes of treatment which mainly include Cyberknife and hyperthermia can be preferred over others, because of their non-invasiveness and more focused way of operations.

Keywords: Glioma; Glioblastoma; Neuro-oncology; Glioma surgery

Introduction and Background

Glioma is a type of brain tumor which originates from glial cells that supply energy and nutrients to the brain and form its supportive tissue. Glial cells also help with the maintenance of blood brain barrier. [1] There are four types of glial cells in the central nervous system namely Astrocytes, Oligodendrocytes, Microglial cells and Ependymal cells. [2]

The types of glioma are: [2]

Astrocytoma: That originates from astrocytes and includes simple Astrocytoma, anaplastic Astrocytoma and Glioblastoma.

Ependymoma: That originates from ependymal cells and includes anaplastic Ependymoma, Myxopappilary Ependymoma and Subependymoma.

Oligodendroglioma: That originates from oligodendrocytes and includes Oligodendrogliomas, anaplastic Oligodendrogliomas and Oligoastrocytomas.

Gliomas are the most common primary intracranial tumor, representing 81% of malignant brain tumors. [3] The prognosis is usually very poor and the mean survival time is only 18 months. The prognosis of patients depends on age, histological features of the tumor, Panofsky performance status and the resectability of the tumor. [4] Glioblastoma is the most common histological subtype, having a five-year survival rate of around 5%. [5] A survey carried out by a multi-center study performed in China in 2006 showed that the incidence of primary brain tumor was 22.52/100,000 and Glioma accounted for 29.78% of all the cases. [6] While glioma is the most common primary brain tumor in adults, astrocytoma is the most common type of glioma. [7] In Pakistan, Astrocytic tumors are the most common of the brain tumors (69.4%). Glioblastoma multiforme forms the largest subtype (40.4%) with a mean age at diagnosis being 47.1 years. [8]

Glioblastomas can also be divided into two types: Primary and secondary Glioblastoma. Primary Glioblastoma occurs in adults older than 50 years of age, characterized by Epidermal growth factor receptor gene amplification and deletion of Phosphatase, Tensin homolog gene and p16. Secondary Glioblastoma occurs in younger patients as low grade or anaplastic astrocytomas and takes years to transform into Glioblastoma. These tumors are characterized by mutations in p53 tumor suppressor gene, amplification of Platelet derived growth factor receptor gene, abnormalities in p16 and retinoblastoma pathway. [4]

Patients having gliomas present with a variety of symptoms, the most common of which are headache, seizures, personality changes, weakness in arms, face or legs, numbness and problems with speech. Other symptoms may include nausea or vomiting, loss of vision and dizziness. Sometimes the gliomas may be slow growing and symptomless and may be diagnosed as an incidental finding on a routine checkup. [7] The diagnosis is usually suggested by magnetic resonance imaging (MRI) and computed tomography (CT) which shows a heterogeneously enhancing mass with edema in the surrounding area. . Positron emission tomography is also being evaluated for its usefulness in diagnosis and monitoring response to therapy. [4]

Treatment of glioma

The common treatment options for a patient with glioma include surgery and/or radiotherapy, chemotherapy and hyperthermic therapy. The treatment starts with general medical management which includes control of seizures, reduction of peritumoral edema, and prevention of venous thromboembolism, fatigue and cognitive dysfunction. [4] Definitive modes of treatment are comprehensively described in the review.

Literature Review and Discussion

Conservative modes of treatment

Surgery: For brain tumors, surgical resection is usually the initial approach to obtain tissue for verification of diagnosis, relieve symptoms, and decrease pressure on the brain or spinal cord and to

How to Cite this Article: Ul-Haq F, et al. A Review of Conservative and Latest Techniques of Treatment of Glioma. Ann Med Health Sci Res. 2018;8:292-295

decrease the size of mass for further management. This is the reason why, starting tumor management with surgery improves outcome. Although care has to be taken so that healthy tissue is not damaged during resection. Many tumors are already invasive making isolated removal of abnormal tissue difficult and requiring additional therapies. [9] A resection may be "gross total" or "subtotal". Gross total is when there is no visible tumor on brain scan done post-surgery and if there is some part seen, it is subtotal. [10]

In a study from United States of America (USA) in which there were 1229 patients with Glioblastoma multiform, 78% of them had resection of their tumors at the cancer center between the period of June 1993 and December 2012. Among the patients, 876 (71%) had complete resection while 353 (29%) had less than 100% resection. Patients who had complete resection showed a longer median survival time (15.2 months) than those who had a less than complete resection. The overall complication rate was 21% in the group with 100% resection and 28% in the group with less than 100% resection [11] [Table 1]. From the data of this research we get this very clearly that total resection have shown high survival duration of 15.5 months with less complication as compared to sub-total resection. [11]

Surgery + Chemoradiotherapy: This is a common way of treatment in which surgery is used as a mode of treatment in adjunction with chemoradiotherapy. Chemotherapy is administration of drugs to slow down or even stop rapidly dividing cells from growing. It may be used as a primary treatment, before another therapy (to shrink a tumor), after another therapy (to destroy remaining tissue) and to relieve symptoms of advanced cancer. It may be delivered by oral drugs or parenterally (intravenous, topical or via a lumbar puncture). When chemotherapy drug travels in our bloodstream to reach the cells it is called systemic and when chemotherapy drugs are directed to a specific area of the body, it is called regional chemotherapy. [12]

Radiotherapy on the other hand is using high-energy beams to kill tumor cells. Radiations may be in the form of X-Rays, Gamma rays or charged particles. Moreover these may be administered from outside or from something placed inside the body. It may be used alone or in many cases (like high grade gliomas) it is used in combination with surgery and/or chemotherapy. The type of radiation prescribed depends on many factors like the type and size of cancer, the location of cancer in the body and the patient's general health status. [10]

In a study where surgery was the mainstay of treatment with chemoradiotherapy, 294 patients from Ohio and 1097 patients from Taiwan were registered, out of which 70.3% and 51.4% had surgical resection with chemoradiotherapy respectively. Majority of the patients getting this combined treatment had the highest survival rate of 1 year. Those who did not receive this treatment had increased risk of mortality (other variables were adjusted) [13] [Table 2]. So this study shows that the survival after one year of treatment with surgery + chemo radiation in two different regions of the globe is same. It also shows that regional factor does not have effect on treatment. [13]

Radiotherapy: Radiation therapy or radiotherapy as described previously is a way of using high-energy radiation to kill cancer cells. There are many types of radiations used for the treatment of cancer, like X-Rays, Gamma rays and other charged particles. It has been estimated that around half of all cancer patients receive some type of radiation therapy sometimes during their treatment. Radiotherapy kills the cancer cells by damaging the cellular Deoxyribonucleic Acid (DNA), either directly or by forming charged particles which ultimately damage the DNA. When DNA of a certain cancer cell is damaged beyond repair, the cells stop dividing, die and eliminated naturally from the body. Normal or non-cancerous cells can also be damaged by these radiations; these are the side-effects of this method of treatment. The amount of radiation that our normal tissues can receive safely is known by the doctor and before starting the treatment, all this potential damage are taken into consideration by the medical team, which helps them to make a right decision regarding the treatment. Radiation therapy can be used for curative as well as palliative intent. [10] Radiotherapy usually comes into play after surgery in high-grade gliomas. Radiotherapy is also very important in treating gliomas which are located in places where surgery is not a safe option, and also for the treatment of recurrent gliomas. [14]

There are three types of radiotherapy used in the patients of gliomas [Table 3]. In a study done in 2002, radiotherapy was used as a mode of treatment in which 343 (91%) eligible and evaluable patients followed up for at least 50 months with an average of 74 months. No significant difference in terms of survival without recurrence (58% for the low-dose arm and 59% for the high-dose arm) showed that low dose of radiation has a good percentage of survival without recurrence or the survival with recurrence (47% and 50%) between the two arms of the trial. So we can conclude that the difference in intensity of radiation does not significantly affect the outcome. One thing should be kept in mind that radiation itself is dangerous and it is frequently observed that treating one tumor with radiation ended up getting another untreatable complication [15] [Table 4].

Table 1: Type of resection, survival duration and overall complications.

Total number of patients (since 1993 – 2012)	Type of resection		Survival duration	Overall complications
1229	Total resection (71%)	876	15.2 months	21%
	Sub-total resection (29%)	353	8.8 months	28%

Table 2: Surgical resection + chemoradiotherapy and survival rate of patients after one year.

Patient who met the inclusion criteria		Patient who received surgical resection + chemoradiotherapy	Number of patients survived after 1 year of treatment	Patients not treated hazard ratio 95% confidence interval	
Ohio	294	207	151 (73%)	5.03	CI: 3.61-7.02
Taiwan	1097	564	414 (73%)	1.49	CI: 1.31-1.71

Table 3: Types of radiotherapy.

Type	Description
Internal radiation with the glial site radiation therapy system	After the removal of tumor mass surgically, liquid radiation is delivered to the edges of tumor's hole through a catheter. This liquid radiation targets the places in and around the tumor site where cancerous cells may be present. It emits a precise amount of radiation for some days.
External beam radiation therapy	This is the most common type of radiation therapy used for the treatment of brain tumor; it can be directed to a localized area of tumor or to the whole brain.
Stereotactic radiosurgery	Stereotactic radiosurgery is a form of radiation therapy in which narrow beams of radiation coming from different angles deliver radiation to a brain tumor.

Table 4: Comparison of dose and outcomes of treatment.

Total number of patients	Eligible and evaluable patients followed up for at least 50 months	Outcome of treatment	High dose (59 Gy for 6.6 weeks)	Low dose (45 Gy for 5 weeks)
379	343 (90%)	Survival with recurrence	50%	47%
		Survival without recurrence	59%	58%

Table 5: Comparison of cost among different modes of conservative modes of treatment.

Total number patients included	Types of treatment	Survival Duration	Average total costs in the 6 months
2272	Group A (Temozolomide + surgery) (3.9%)	331	$106,896
	Group B (Temozolomide + Radiation therapy + Surgery) (37%)	426	$138,767
	Group C (Only surgical) (45.3%)	529	$79,099

Table 6: Outcomes in patients after Cyberknife therapy.

Total number of patients	Number of patients with glioma	Number of patients with successful outcome	Number of patients with radiological improvement on MRI			Post-radiation changes	
			30			Acute	Sub-acute
251	34	31 (90%)	Stable	30% reduction in tumor size after follow-up	Disease increased	13 (10%)	2 (1.59%)
			17 (55%)	11 (32%)	2 (2%)		

Table 7: Tumor size before and after radiotherapy + chemotherapy and hyperthermia.

Total number of patients	Groups of patient (15 patients each)	Tumor size (diameters in cm)	
		Before treatment	After treatment
30	Control Group (received radiotherapy and chemotherapy)	5.13 ± 1.36	6.00 ± 0.13
	Hyperthermia Group	4.99 ± 1.52	2.80 ± 0.24

Discussion

A comparison of cost among different conservative modes of treatment

Ray et al. in their study showed the comparison of three different ways of treatment and the cost and survival duration in which a total of 2272 patients met the inclusion criteria, 3.9% received the chemotherapy drug Temozolomide + surgery, 37% received Temozolomide + radiation therapy and surgery and 45.3% of patients received surgical treatment only. The median survival was 456 days, ranging from 331 days for group A to 529 days in group B. In the cohort of patients receiving both radiation and Temozolomide with surgery, the median survival was 426 days (14.2 months). The average total cost in the six months post index was $106,896 for group A, $138,767 for group B and $79,099 for patients who received neither temozolomide nor radiation [16] [Table 5].

This study concludes that the patients receiving Surgery + chemotherapy and Surgery + chemoradiotherapy show high cost and less survival duration when compared with patients who only go through surgery. [16]

Some latest modes of treatment of glioma

Cyberknife: This is one of the most newly developed forms of radiological surgeries. Being a non-invasive procedure it delivers great doses of accurately targeted radiation for treating tumors (and some other medical conditions). Cyberknife consists of a robotic arm, flexibility of which enables it to treat areas that are not easily accessible. The second main component is the radiation produced from a small linear particle accelerator. There are three steps involved in the entire process: set-up and imaging; treatment planning; and the actual procedure. Main components include Robotic mounting, Image guidance, 6D skull, X sight, Fiducially, Synchrony and Frameless. [17]

Since August 2001, the Cyberknife system has Food and Drug Administration clearance for treatment of tumors in any location of the body like pancreas, liver, prostate, spinal lesions, head and neck cancers, and benign tumors. Due to this great accuracy by the device there is potential of dose escalation and a subsequent increase in effectiveness, particularly in local control rates. However, the studies are so far limited in scope and more research will need to be done in order to show any effects on survival. [18]

In a study on Cyberknife from Karachi, Pakistan, there was a total 251 patients, out of which 34 patients had glioma. Cyberknife treatment was applied on these glioma patients and after the treatment 55% showed stability on MRI, 32% showed decrease in tumor size while 2% showed an increase in the disease [19] [Table 6].

Cyberknife has proved to be excellent as far as the outcomes of treatment is considered. The radiation of Cyberknife is focused with very less complications and the advantage of using high dose of radiation is that there are chances of cure with very less duration of exposure. [19]

Hyperthermia: This is a type of cancer treatment in which high temperatures up to 113° Fahrenheit is applied on body tissue as it can kill and damage neoplastic cells somewhat specifically, leading to tumor shrinkage. Hyperthermia may be “local” in which heat is applied to a small area, “regional” in which heat is applied to larger tissue area or “whole body”. Different types of energy may be used to apply heat like microwave, radiofrequency and ultrasound. There are many heats delivering techniques like focused ultrasound, Infrared Sauna, microwave heating and induction heating. [9]

In a study by Sun J et al. thirty glioma patients were included and randomly divided into control and hyperthermia groups; with 15 patients in each group (patients with grade III–IV primary glioma did not receive concurrent chemotherapy and radiotherapy, while recurrent glioma patients underwent both). Patients in the control group received both radiotherapy and chemotherapy but not hyperthermia. All 30 patients were involved in the final analysis. They also underwent head

CT or MRI examination before and after hyperthermia treatment (with duration of three months in between) to measure tumor diameter. There was no significant difference in tumor diameter between the two groups before treatment, but at three months after treatment tumor diameter in the hyperthermia group was significantly smaller than that in the control group [20] [Table 7]. The tumor size showed a very surprising decrease in patients receiving hyperthermia therapy as compared to patients receiving chemoradiotherapy only. There rate complications were also low in the hyperthermia group. [20]

Conclusion

For summarizing this whole review we can come to the point that among conservative modes of treatment, surgery outstands because of very high success rate (especially after total resection) and cost-effectiveness but other modes of treatment of glioma have also shown wonderful outcomes. Some latest techniques like Cyberknife and hyperthermia are non-invasive, more focused ways of treating the tumor with excellent post-treatment results, so these can be preferred over conservative modes of treatment after assessing the practicality and effectiveness of the approach.

Conflict of Interest

The authors disclose that they have no conflicts of interest.

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