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A Review of Innovated Treatment for Gliomas

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Abstract. Brain tumors are difficult to be totally cured , and also associated with high rates of mortality and morbidty, therefore the therapy is always a hot issue. This review introduces glioma treatment techniques through literature summarization and qualitative analysis. According to the data, technologies that can improve median survival and potentially substitute contemporary techniques during the treatment, including photon therapy, and hyperthermia. Moreover, some techniques can improve the accuracy and safety of surgical, such as Intraoperative Neuromonitoring and Neuronavigation During Resection. Other treatment methods, such as gene therapy and immunotherapy, are feasible based on their principles. However, their current effects have not reached expectations, so they are not widely used at this stage, and further innovation and experimental proof are needed.

Keywords: gioma, treatment, glioma surgery, radiotherapy, chemotherapy

1. Introduction

Glioma is a common central nervous system (CNS) tumor that originates from glial cells [1], and it is a kind of lethal tumor. According to the classification of the World Health Organization(WHO), gliomas can be divided into 1 to 4 grades based on anaplasia, mitotic activity, proliferation, necrosis, and other kinds of histopathologic characteristics. Grades 1 to 2 is low-grade gliomas(LGGs). Grades 3 to 4 is known as high-grade gliomas(HGGs). Anaplastic astrocytoma (grade 3) and glioblastoma (GBM) (grade 4) are tumors that have infiltrative nature[2], so those are impossible to resect completely, especially GBM, it is the most lethal brain cancer. The widely used treatments are surgery, chemotherapy, and radiation therapy, and the therapeutic effect is very significant and can prolong the median survival of LGG patients. However, for patients with HGGs, the effect of those therapies is limited, GBM tumor cells even developed resistance to radiotherapy and chemotherapy, thus treatment for HGGs requires innovation to improve the 5-year survival rate and life quality of patients. This review introduces and compares some innovations for the treatment of gliomas, ordering to find out which is more suitable to be as a new treatment that can be widely used. Those techniques include neuronavigation, and Intraoperative Neuromonitoring During Resection (IONM), which improve the accuracy of surgery, and ensure patient safety. Seed implantation, gamma knife, Photon Radiotherapy, and Proton radiotherapy, are the innovation of conventional radiotherapy. They use different energies to substitute X-rays, reduce the toxin for normal cells, and improve the efficiency of radiotherapy. As well as other prospective treatments like gene therapy, immune therapy, hyperthermia, and AI technique, for example, machine learning, which is still in clinical trial or is rarely used in the present treatment.

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2. Techniques for the therapy of gliomas

2.1. Emotional therapies and their innovation

2.1.1. Surgery. As for gliomas, surgery is the most efficient way to decrease the size of tumors, and relieve symptoms, this is the reason why having surgeries before other treatments for gliomas. However, the central nervous system is significant, every part has its own function, therefore surgical strategy is important. Magnetic Resonance Imaging (MRI) can be used to visualize different areas in order to locate the general position of tumors, but it is not enough, there are more techniques that can be used in treatments of malignant gliomas.

2.1.2. Neuronavigation. Neuronavigation systems are extensively used in the surgery of brain tumors in order to identify the boundaries between tumor cells and normal cells, and minimize inaccuracy. The principle of neuronavigation is to establish the relationship between device space and image space, thereby providing the correlation between the data of digital image and the anatomical structure, to show the corresponding position images in real time.[3] By this technique, today's neuronavigation system can reach up to the accuracy of 2mm[3]. However, there are also limitations concerning neuronavigation, brain shift, and the deformation of brain during the surgery can influence the accuracy of neuronavigation [4]. Nevertheless, it can increase the safety of surgery, it is really useful for surgeons.

2.1.3. Intraoperative neuromonitoring during resection. IONM techniques include direct electrical stimulation (DES), this technique uses direct electrical current to stimulate the cortex to localize functional areas; somatosensory evoked potential (SSEP), stimulating a strip electrode which is put in the central sulcus and record the data to determine the location of central gyrus, this could be used for predicting the injury of some vessels; electromyography (EMG), electrocorticography (ECoG), this can be used for detecting spontaneous and stimulus-elicited waves; and motor evoked potential (MEP). Using the combination of those techniques can monitor the dangerous state of neurons, and reflect whether there is ischemia, thermocoagulation, and so forth in real time.[5] Therefore surgeons can stop the surgery to protect neurological functions, to avoid damage.

2.1.4. Radiotherapy. Using high energy beams like X-rays, gamma-rays, or charged particles to kill cancer cells, those high energy beams can damage the DNA of tumors, stopping cells from dividing.[6] However this technology also has its own disadvantages, the radiation of high energy beams can cause damage to normal cells, so many advanced radiotherapies emerged, aiming to improve the accuracy and the safety of radiotherapy, reducing the damage caused by radiation.

2.1.5. Seed implantation. It is a widely accepted branch of therapy, which is based on the operation of implanting radioactive seeds around or inside the tumor under the guidance of CT and MRI. Some radioactive particles such as iodine-125 can damage the DNA of cancer cells.[7] Because these seeds are implanted sites,thereby reducing tumor toxicity to normal cells. This improves the safety and accuracy of radiotherapy. Yidu Central Hospital of Weifang [7] selected sixty-six patients with gliomas, and they were randomly divided into two groups, the control group (surgery alone) and the observation group(surgery with seed implantation), with 33 patients in each.MRI examination was used to observe tumor volumes, and after 3 months, the evaluation shows that the outcomes of the observation group were much better than the control group. This has shown that a seed implantation is an efficient approach to dealing with gliomas.

2.1.6. Gamma knife. The Gamma knife is a kind of radiotherapy that uses gamma-ray released by 60Co, the principle of the gamma knife is similar to the focusing of the magnifying glass, the temperature of focus is high. However, the temperature of places outside the focus is normal.[8] The

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Gamma knife use gamma-ray with the combination of CT, MRI, computer, and biological radiation to destroy the tumors, aims to resect the tumors and improve the safety. According to the data of Gamma Knife Center Tilburg from 2002 to 2015[8], 92 patients were treated with gamma knife, and the result showed that tumor control was 50% in LGGs and 27% in HGGs, median progression-free and overall survival were 10.5 and 34.4 months respectively, no severe side effects happened after treatment of gamma knife. This has shown the gamma knife can improve the survival rates of patients and can safely be used to treat gliomas.

2.1.7. Energy Modulated Photon Radiotherapy

Energy Modulated Photon Radiotherapy(EMXRT) is a novel kind of radiotherapy. Using different photon energy beams to destroy tumors. The first step is to choose the energy of beams by an energy selector, lower energy photon beams (<6MV) can be used for normal radiotherapy treatment to combine with other treatments, in order to improve the life quality of patients. High energy photon beams(>10MV) are used for treating deep-seated tumors, because penetration is proportional to energy, higher energy beams can destroy the tumor easier.[9] However the disadvantage is the same as other kinds of radiotherapies, high energy can cause more damage(exit dose outside the target place), and even more problems like neutron contamination. According to the data from the American National Cancer Data Base from 2004 to 2013[10], 49405 patients with primary gliomas were treated with Photon therapy. After observation of 62.1 months, the median and 5 year survival were 29.7 months and 35.5% respectively. This means photon therapy has a positive effect on the treatment of gliomas.

2.1.8. Proton therapy. Proton therapy is an emerging kind of radiotherapy, and the facilities of proton therapy are rapidly increasing. Also, the data of the American National Cancer Data Base from 2004 to 2013 [10], 170 patients with primary gliomas were treated with proton therapy, the median and 5 years of survivals were 45.9 months and 46.1%, much higher than the data of photon therapy. The principle of proton therapy is to accelerate the nucleus of hydrogen atoms by cyclotron accelerator or synchronous accelerator, then using an extremely fast speed to penetrate into human body and reach the specific place of cancer cells, the speed suddenly decreases and stops, releasing energy and killing tumor Cells. Considering the physical characteristics of proton, the dose used for proton therapy is smaller, so this is more safe then other kinds of radiotherapies, bringing less damage.[11] However, there are also some inadequacies. Thurin et al. (2018) summarize the results of studies published between 1990 and 2017 on proton therapy for low grade gliomas. Proton therapy was found to cause side effects like local erythema, alopecia, headache and fatigue, and the price of proton therapy was much more expensive than other types of radiotherapies. Even though proton therapy is advanced and potential, the available clinical data on this are still limited, further clinical trials are still needed.

2.1.9. Chemotherapy. Chemotherapy can be used as initial treatment or after surgery, drugs for the treatment of gliomas include nimustine (ACNU), carmustine (BCNU), lomustine (CCNU), and semustine (MeCCNU) [12]Those drugs can slow down or even stop the dividing of tumor cells by damaging the DNA. Chemotherapy is widely used all over the world. However the side effect is obvious, the poor penetration of most chemotherapeutics across the blood-brain barrier makes more doses is needed, so more damage can be caused. Those chemotherapeutics can cause bone marrow suppression, leading to immune system diseases such as neutropenia, thrombocytopenia and lymphopenia[13]. The decrease in immunity will makes it difficult to implemented radiotherapy and chemotherapy, thus forming a vicious cycle.

2.2. Advanced and perspective therapies

2.2.1. Hyperthermia. Using the temperature up to 113 Fahrenheit on the body tissue to kill tumor cells specifically, and the heat can be applied to a small area, different types of energy can be used, for example, microwave, radiofrequency, and ultrasound [6]. One experiment [14] randomly divided 30

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people with grade 3-4 glioma into the hyperthermia treatment group and control group(underwent conventional radiotherapy and chemotherapy), for 3 months after that, patients were observed by CT or MRI every month. The result has shown that in the group of hyperthermia, the necrosis of 80% of tumor tissues was obvious, and the diameter of tumors decreased, however in the control group, there wasn't any evident necrosis of tumor tissues and tumors were still growing. Therefore hyperthermia is an effective way to be used in the treatment of gliomas. However hyperthermia also has its limitation, benign brain tumors do not sensitive to heat, this means hyperthermia can be effective in the treatment of malignant HGGs, but not that effective when dealing with benign tumors.

2.2.2. Gene therapy. The principle of gene therapy is to deliver genes through different kinds of vectors to patients' bodies, then revert the migration and proliferation of tumors and even lead to the death of tumor cells.[15]The gene targeted in tumor cells includes p53 (a kind of tumor suppression gene, the frequent loss or mutation of it can cause malignant gliomas), Herpes simplex virus type 1 thymidine kinase gene (HSV-tk) (a kind of enzyme that causes toxic effect with the combination of a drug named ganciclovir),and interleukins and interferons[15](the effects of those two genes are evoking immune response). And the normal vectors include liposomal vector, cell vector and, viral vehicle. A clinical trial conducted interferon beta gene therapy on 5 patients who had malignant glioma. 4 patients were detected and evaluated after 3 months, and the result was that 2 patients had a tumor reduction of 50%. Another trial gave HSV-tk gene treatment to 8 patients, and the result was that 2 patients had a reduction of the tumor by more than 50%[15]. Those mean gene therapy is potential and effective in some cases, but there is still problem like which vector to use,and how can the efficiency of gene therapy be improved, still needed to explore.

2.2.3. Machine learning. In the domain of gliomas research, the processing of images and data is always a pressing issue. The emergence of machine learning accelerated the process of data processing, which brings benefits to the treatment of gliomas. Machine learning is a kind of artificial intelligence(AI), having the ability to create algorithms, recognize, classify the tumor and even predict the development of cancer cells by analyzing data. In 2006, Machine learning was combined with in imaging technique, in 2009 it was widely used in the analyses of sequence data, and in 2015 neural network was used in the treatment of gliomas[16]. Nowadays, the main application of machine learning in the field of gliomas include feature selection, automatic segmentation, recurrence, biomarkers prediction, grades classification and prognosis prediction[16], which brings benefits to the diagnosis and treatment of gliomas. However, challenges still exist, the challenges in data, for example, lack of annotated data, the challenges in algorithm aspect, the challenges in clinical application, are still problems to solve.

2.2.4. Immunotherapy. The principle of immunotherapy is to activate the immune system to eliminate tumor cells. [17] Various immunotherapies for gliomas are still in the stage of the experiment, so there is a lack of clinical data to analyze. Immunotherapies, such as vaccines, checkpoint inhibitors and T cell therapy, have potential in the treatment of gliomas due to their therapeutic advantages. Among them, vaccine treatment is mainly based on the fact that it can induce the generation of specific B and T cells, releasing cytokines and antibodies. Checkpoints are molecules that increased when T cells start to attack infected or cancerous cells, and those are used to prevent the attack from damaging normal cells. Moreover, research showed that tumor cells often possess checkpoints, for example, CTLA-4 and PD-L1, which aims to suppress the responds of the immune system. Therefore, people use checkpoint inhibitors to make drugs in order to unleash the immune system's attack on tumor cells. T cell therapy focuses on the adoptive transfer of TCR-transgenic T cells[17]. All those treatments lack clinical trials and are in the stage of the experiment, therefore whether immunotherapy is an effective treatment for gliomas is still questionable.

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3. Discussion

3.1. Chemotherapy+ surgery vs chemotherapy + surgery + radiotherapy vs surgery only

The study of Ray et al. compared the outcomes and cost of those three combined treatments, in the study, group 1 received Temozolomide+surgery, and group 2 received Temzolomide + surgery +radiotherapy, group 3 received surgery only. The result for median survival was 331days, 426 days, and 529 days respectively, the average cost was $106890, $138767, and $79099 respectively.[6]

This study shows that receiving chemotherapy+surgery is the most inefficient treatment for gliomas, surgery only is the most effective way, and according to the median survival, those patients should be patients with HGGs, the tumor cells of HGGs show higher resistance to chemotherapy and radiotherapy, also the damage and myelosuppression caused by chemotherapy and radiotherapy can have an inverse impact on patients. Therefore, for patients with HGGs, combined treatments like surgery plus chemotherapy or conventional radiotherapy may have a destructive impact on patients.

3.2. Re-resection vs chemotherapy vs re-irradiation vs gene therapy (Hsv-tk) for recur of glioblastoma (GBM) and astrocytoma (AA)

According to the data from the National Institutes of Health, the USA between 1987 and 2000[18], the median survival for GMB was 14-50 weeks, 19-28 weeks, 34-47 weeks, 29weeks for the patients who received re-resection, chemotherapy, re-irradiation, and gene therapy respectively. The median survival for AA was 55-88 weeks, 44-81 weeks, 52-105 weeks, and 37 weeks respectively. Those data have shown that gene therapy(Hsv-tv) has a similar effect to chemotherapy, and the main side-effects are constipation and sedation[18]. Therefore it can safely be used in the treatment of gliomas according to this, but this technique still need to be innovated because the efficiency does not reach our expectation, the problem should be the usage of vectors, the vectors that exist now show low efficiency to delivery gene, some vectors also have a side effect on patients, so the delivery way is significant to the efficiency, which should be innovated.

3.3. Photon therapy vs proton therapy

According to the data from American National Cancer Data Base from 2004 to 2013[10], for patients with primary gliomas, the median survival for photon therapy and proton therapy was 29.7months and 45.9 months, this shows a significant difference between those two therapies, meaning proton therapy is more effective.

According to those comparisons, sometimes the combination of diverse treatments can have the opposite effect. And some innovations in conventional treatments show better outcomes, for example, new techniques used in surgery, and novel kinds of radiotherapy, which have already been used in the treatment of some gliomas. However, some advanced therapy that seems potential according to their machanism, for example, gene therapy and immunotherapy, still haven't reached up to expectation, therefore advanced techniques are needed to improve their efficiency. So effective treatments for LGGs include surgery, radiotherapy, and chemotherapy, cause those tumor cells are easier to be restricted, other therapies may costly(proton therapy) or have the same (or less) effect as conventional ways(gene therapy and hyperthermia) for tumors grades1 and 2. For HGGs, surgery, hyperthermia, and proton therapy show better outcomes, conventional ways like chenmotherapy and radiotherapy have limited effect on HGGs, and the side effect even reduces the median survival of patients.

4. Conclusion

In conclusion, for LGGs, the combination of surgery, radiotherapy, and chemotherapy is efficient and has a high success rate. For HGGs, innovative techniques like proton treatment and hyperthermia show better outcomes. This review paper also has some limitations, there are still other techniques not mentioned above, such as cyberknife and other kinds of gene therapies, immunotherapies. In addition, limited clinical data of proton therapy, gene therapy, and immunotherapy lead to inaccurate results.

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