Stereotactic Radiosurgery in the Treatment of Glioblastoma Multiforme: Current Status of Technology and Potential Role of Microbeam Radiosurgery

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Abstract

Stereotactic radiosurgery is an emerging treatment option offered to patients with glioblastoma (GB). Radiosurgery is performed as an outpatient procedure and provides a safe and effective non-invasive treatment for focal GB. High-energy beams originating from cobalt sources placed into a helmet-shaped device (Gamma Knife®, Elekta) or generated by a linear accelerator (LINAC), rotating on a gantry (X-Knife®, Novalis), or maneuvered by a robotic arm (CyberKnife®, Accuray) are delivered with submillimetric accuracy to a selected intracranial target. Treatment accuracy is assured by image-guided volumetric CT and MR studies complemented with advanced metabolic neuroimaging techniques, such as PET-CT. Some authors suggest radiosurgery as a salvage treatment in patients with recurrent GB to avoid further surgical procedures or as a complement to conventional fractionated radiotherapy. This paper reviews the current role and applications of stereotactic radiosurgery in the treatment of GB, illustrating also an emerging experimental technology, microbeam radiosurgery, which is close to being welcomed into the clinical field.

Categories: Radiation Oncology, Neurosurgery
Keywords: synchrotron-generated microbeams, cyberknife, imrt, gamma knife, brain, glioblastoma, stereotactic radiosurgery

Introduction And Background

Glioblastoma (GB) is the most common malignant primary brain tumor in adults and carries a dismal prognosis. Microsurgical resection followed by external beam radiotherapy (EBRT) and concomitant/adjuvant temozolomide chemotherapy is considered a standard initial treatment for GB [1]. Despite intensive research aiming to develop new diagnostic and therapeutic modalities designed to target GB, survival is only slightly better today in comparison to early days when neuroimaging, microsurgery, radiotherapy, and chemotherapy had much less to offer [2-3]. Overall, even the combination of the most aggressive treatment options currently available is associated with limited survival: patients who live longer than two years after diagnosis remain an exception. Progressive neurological deterioration and death are caused by recurrent disease, which typically occurs near the tumor resection bed [4-5]. Radiosurgery (and concomitant/adjuvant temozolomide chemotherapy), while controversial, is an increasingly employed option to treat GB patients, especially in the setting of recurrent disease [6-7]. A fast and safe procedure that does not require hospitalization, radiosurgery also does not interfere with chemotherapeutic schedules. The aim of this paper is to provide a concise update on the

radiosurgical techniques available to treat GB and briefly illustrate an emerging experimental approach to the treatment of malignant brain disorders based on a novel microradiosurgical technique [8-11].

Review

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is characterized by a steep radiation fall-off outside the target, allowing the delivery of high radiation doses with minimal radiation exposure to adjacent normal structures [12]. By definition, the dose delivered falls from 80% to 20% within 3 mm of the lesion's boundaries. The spatial constraints imposed by this tight dose fall-off are essential in order to preserve delicate nearby neurological structures, while delivering effective doses to the lesion. Another important issue is the delivery rate: a high dose rate increases the lethality of the dose delivered due to its greater interference with intrinsic cellular repair mechanisms during irradiation [13]. Accordingly, normal tissue around the target not only receives a lower dose, but also receives it at a slower rate.

The histological effects that can occur one year after a single-stage CNS irradiation are dose-dependent [14]. Vascular changes (telangiectasia, thrombosis, fibrinoid necrosis of vessel walls, hyaline degeneration, and hemorrhage) can be observed one year after a single-stage delivery of 20 Gy. Doses greater than 25 Gy also induce marked white matter changes, ranging from demyelination to myelomalacia. A single-stage delivery of 50 Gy causes astrocytic swelling without changes in neuronal morphology or breakdown of the blood-brain barrier at 12 months, whereas 75 Gy induces earlier morphological changes: astrocytic swelling appears within four months, followed by necrosis, breakdown of the blood-brain barrier, and hemispheric swelling. At a dose of 120 Gy, astrocytic swelling occurs within one week of irradiation, and necrosis can be seen at four weeks [14].

Image guidance

Image guidance is the basis for the accurate delivery of a large number of radiant energy beams to an intracranial target. These beams can be painted over or cross-fired through the target depending on the treatment planning facilities of the device being used. The head of the patient is either held by a stereotactic frame affixed to the skull providing a fixed position, or contained by a thermoplastic mask allowing modest movements, which are detected and compensated for in real time. These different treatment modalities are referred to as frame-based and frameless radiosurgery, respectively.

Until the introduction of the CyberKnife® (Accuray Incorporated, Sunnyvale, CA) in the late '90s, radiosurgery was delivered only through frame-based techniques. The introduction of an image-guided robotic arm positioning a light-weight linear accelerator around the target has paved the way to a completely non-invasive modality to deliver brain radiosurgery and to the consequent expansion of this treatment to other areas of the body [15-16].

Frame-based radiosurgery

Radiosurgery was developed by Lars Leksell as a technique to deliver high-energy beams to a selected intracranial target with awesome precision. Leksell explored several irradiation sources before resorting to the use of cobalt issuing gamma rays. The first radiosurgical device largely used for clinical treatment was therefore called Gamma Knife® (Elekta AG, Stockholm, Sweden).

The current Gamma Knife System (GKS) utilizes 192 individual ^{60}Co gamma ray sources, placed within a helmet-like configuration. A stereotactic frame is required to immobilize the patient's head and precisely direct the cross-fired beams to the target. Head fixation is an essential step that provides the spatial tri-dimensional references needed to deliver the therapeutic beams with

submillimetric accuracy. All of the Gamma Knife ^{60}Co sources are arranged in a near-hemispheric array, the beam axes of which all cross a common point in space called the isocenter. Because beam collimation is circular, the high-dose volume at the point of intersection is a sphere. The dose gradient produced by the GKS is so steep that only a few millimeters of displacement would result in a significant decrease in the delivered dose, provided that the treatment volume is not large enough to compensate (e.g. over 10 cc). Conformal GKS treatment of non-spherically shaped lesions, which constitute the vast majority of tumors, is achieved through the use of multiple isocenters, each requiring the patient's repositioning in the GKS helmet. Using the GKS, selected beam trajectories can also be blocked to further improve conformality and normal tissue sparing.

An alternative to the Gamma Knife was developed in the mid-1980s using the conventional linear accelerators (LINAC) available in most large hospitals [17]. Unlike the radioactive cobalt-based Gamma Knife, these LINAC-based systems use generated X-ray beams which do not require or generate any radioactive material. Gantry-based LINAC radiosurgery systems rotate around the target along non-coplanar arcs delivering single beams of high energy radiation (e.g., 6 MV) in an isocentric fashion. Target localization and treatment delivery in gantry-based systems, as with the GKS, requires immobilization of the patient's head with a stereotactic frame. Conformal treatment of non-spherical lesions is performed with multiple overlapping isocenters. In addition, isocenter shapes can be slightly modified by changing the position and the length of each arc.

Conformality can be further improved through beam shaping provided by computer-controlled multileaf collimation. This beam shaping technique, combined with algorithms for dose optimization, is termed intensity-modulated radiation therapy (IMRT) [18]. IMRT can modulate the intensity of each radiation beam, so each field may have a single or multiple areas of high intensity radiation and any number of lower intensity areas within the same field. By modulating both the number of fields and the intensity of radiation within each field, there are limitless possibilities to shape radiation dose to conform to irregular concave surfaces and to produce invaginations in dose distribution, while sparing circumscribed normal tissues. Nevertheless, IMRT is not as spatially precise as radiosurgery.

Frameless radiosurgery

The traditional stereotactic technique developed by Leksell requires fixation of a rigid frame to the patient's skull for head immobilization and target localization. Wearing the frame for more than a few hours is bothersome, and normal levels of weight-bearing by stereotactic frames may reduce their mechanical accuracy [19]. Therefore, frame-based treatments are typically delivered in a single stage and are limited to intracranial and high-cervical targets. Frameless radiosurgery replaces the stereotactic frame with real-time image guidance based on digitally reconstructed skull radiographs extracted from the patient's CT scan, which are overlaid onto the 6D skull X-rays obtained during the treatment [16, 20]. Frameless radiosurgery facilitates the delivery of irradiation in multiple stages improving the tolerance of healthy tissues to the treatment.

The first and most widely used frameless radiosurgical device is the CyberKnife, which uses non-invasive image-guided localization, a light-weight high-energy radiation source, and a robotic arm to deliver accurate and precise irradiation to any region of the body in one or multiple sessions [21]. The treatment planning system of the CyberKnife exploits the robot's sixdegrees-of-freedom maneuverability, allowing non-isocentric targeting that superimposes an overlapping array of up to 1600 beam trajectories on the target (with the latest G4). An inverse planning procedure optimizes the set of beam directions and dose to be used, delivering homogeneous dose distributions that can conform to highly irregular volumes. As a result, the CyberKnife has submillimetric accuracy [22-23] and can be used to treat intracranial lesions as well as extracranial spinal lesions, including intramedullary AVMs and lesions in the chest and abdomen [15] .

The combination of sophisticated real-time image guidance techniques and robotic delivery is the basis of the CyberKnife's precise irradiation delivery. Two X-ray imaging devices using highly sensitive amorphous silicon detectors are positioned on either side of the patient's anatomy and acquire real-time digital radiographs of the treatment site at repeated intervals during treatment. The images are automatically registered to digitally reconstructed radiographs derived from the treatment planning CT. This registration process allows the position of the skull (and thus the treatment site) to be translated to the coordinate frame of the LINAC. A control loop between the imaging system and the robotic arm adjusts the pointing of the LINAC's therapeutic beam to the target. In essence, the robotic arm can follow the changes in the patient's position and preserve the patterns with which the beams traverse the patient's anatomy and intersect within the target. If the patient's treatment position in the camera coordinate system is exactly the same as in the CT study, then the image guidance system makes no positioning correction and the robot moves the LINAC to the original workspace nodes specified by the treatment plan. If the patient moves during treatment or is displaced relative to the CT coordinates at initial setup, the robot adjusts the spatial position and orientation of the LINAC to maintain the position of the beams fixed with respect to the targeting feature (bone or fiducials), thereby ensuring that all beams not only continue to point at the planned target, but also pass through the patient anatomy as prescribed.

Frameless radiosurgery is a novel treatment modality using an advanced image guidance technique that provides accurate and precise delivery in the absence of a rigid frame. That is, frameless radiosurgery removes the need to apply an invasive frame to the patient's skull and also enables the option of treating in multiple fractions. The absence of a frame hanging parallel to the skull base opens the possibility to use a vast array of penetration trajectories through the splanchnocranium, and consequently, the ability to spare the brain and related critical structures more efficiently. The reduced overall brain irradiation, achievable through using beam trajectories penetrating the lower part of the skull instead of the convexity, has not been systematically investigated, but it clearly may represent an advantage in terms of reduced toxicity.

The role of SRS in the treatment of GB

SRS provides a reasonable treatment option in patients poorly fit for open surgery or harboring unresectable lesions. The diagnosis should be verified by a stereotactic biopsy, but the risk of severe bleeding due to the insertion of a needle into the tumor must be considered. In some cases, a convincing diagnostic certainty can be reached by the use of advanced neuroimaging techniques, such as spectroscopy, perfusion, or diffusion studies.

Although a firm consensus has not been reached regarding the role of SRS in the treatment of GB, it has been used to treat GB in the primary setting, as a boost following conventional EBRT, or as a treatment for recurrent GB. The first scenario is rare and applies mainly to GB cases located in surgically inaccessible regions, such as the basal ganglia, thalamus, hypothalamus, or brainstem, and volumetrically amenable to radiosurgical treatment (Figure 1). Patients with severe medical contraindications to general anesthesia or who refuse open surgery can also be treated primarily with SRS (Figure 2). There are currently no reports on the ability of radiosurgery to control GB when performed as a primary treatment. However, this treatment option should be kept in mind and used cautiously, in combination with chemotherapy, in selected cases not amenable to surgery. Figure 1 shows the treatment planning of a patient with a GB located in the hypothalamic region and primarily treated with SRS and chemotherapy. Microsurgical resection of aggressive and infiltrating lesions located in these brain regions is associated with a real possibility of extremely severe neurological complications and death. Single-stage CyberKnife SRS was administered to this patient, achieving local growth control lasting for nine months. The patient illustrated in Figure 2 was also treated primarily with SRS due his poor performance status and his absolute refusal to undergo open surgery. Local growth control was achieved and maintained for about two years.
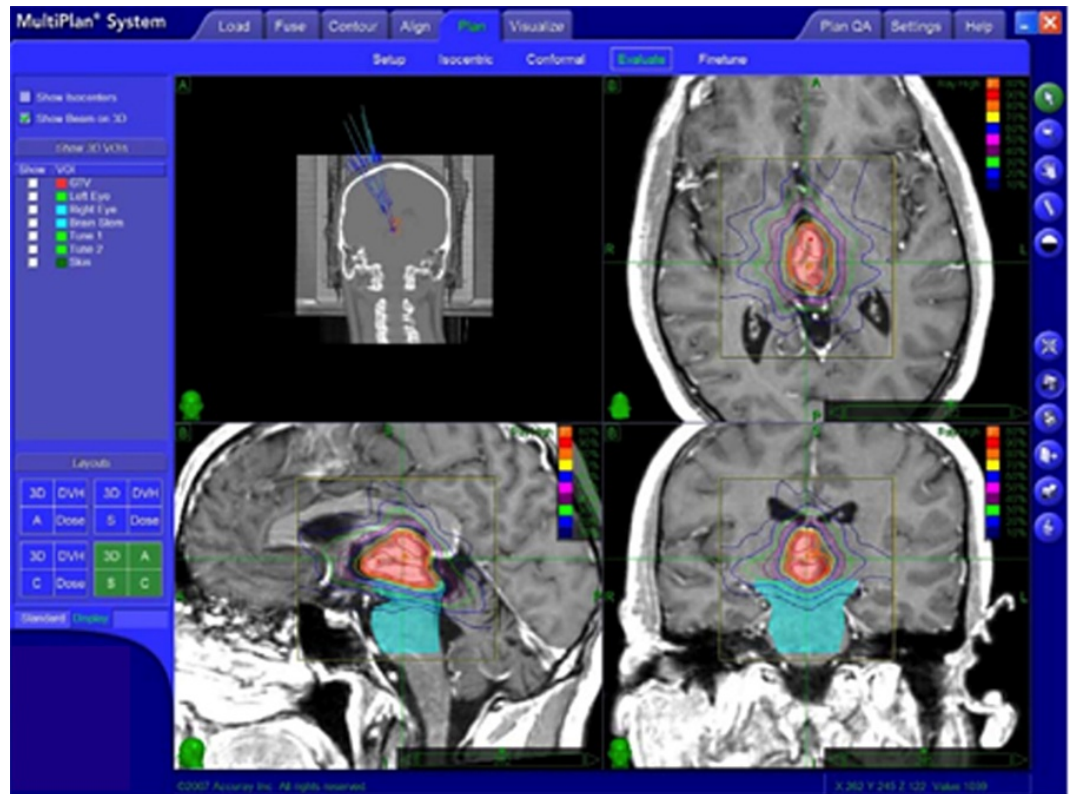
FIGURE 1: Hypothalamic GB treated primarily with CyberKnife SRS.

Sagittal and coronal treatment planning views illustrate well the conformality of the treatment and its ability to spare critical neural structures such as midbrain and hypothalamus located near the lesion.
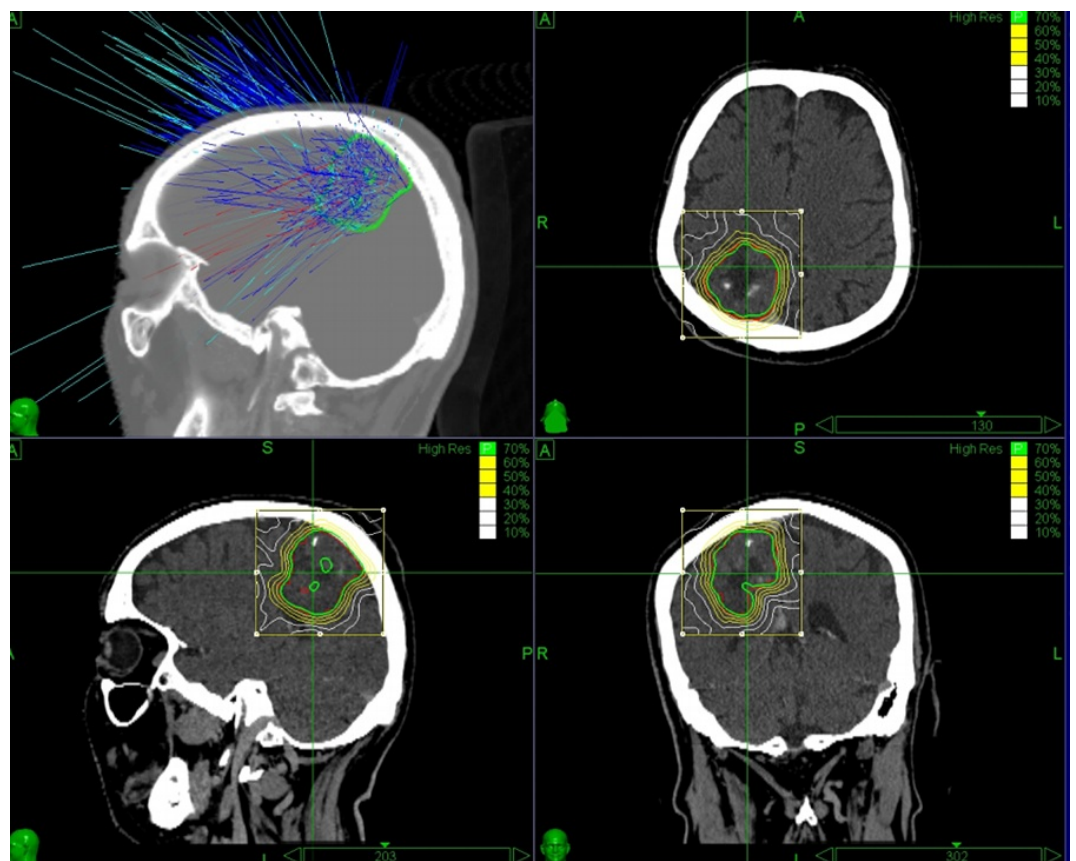
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Several studies have been published recently on the use of radiosurgery as a boost to EBRT or as the primary treatment of recurrent GB. It appears that SRS does not produce any survival benefit when added to conventional radiotherapy but is associated with significant survival benefit when used as the primary treatment for recurrent GB. Several retrospective studies have reported a survival advantage using SRS as a boost before or after conventional radiotherapy [24-27]. However, a large Phase III study on 203 patients failed to demonstrate a survival advantage for the patients who received an additional radiosurgical boost as part of the initial management strategy: the stereotactic radiosurgical group had a mean survival time of 13.5 months, whereas the control group had a mean survival time of 13.6 months [28].

SRS has been consistently reported to be associated with prolonged survival in patients with recurrent glioblastoma [7, 29-30], and it appears to benefit most young patients, as well as patients with good performance scores. Figure 3 illustrates a recurrent GB involving the primary motor cortex near the resection cavity treated with single stage CyberKnife radiosurgery. Local growth control was achieved and maintained for over 12 months. The treatment was well-tolerated.
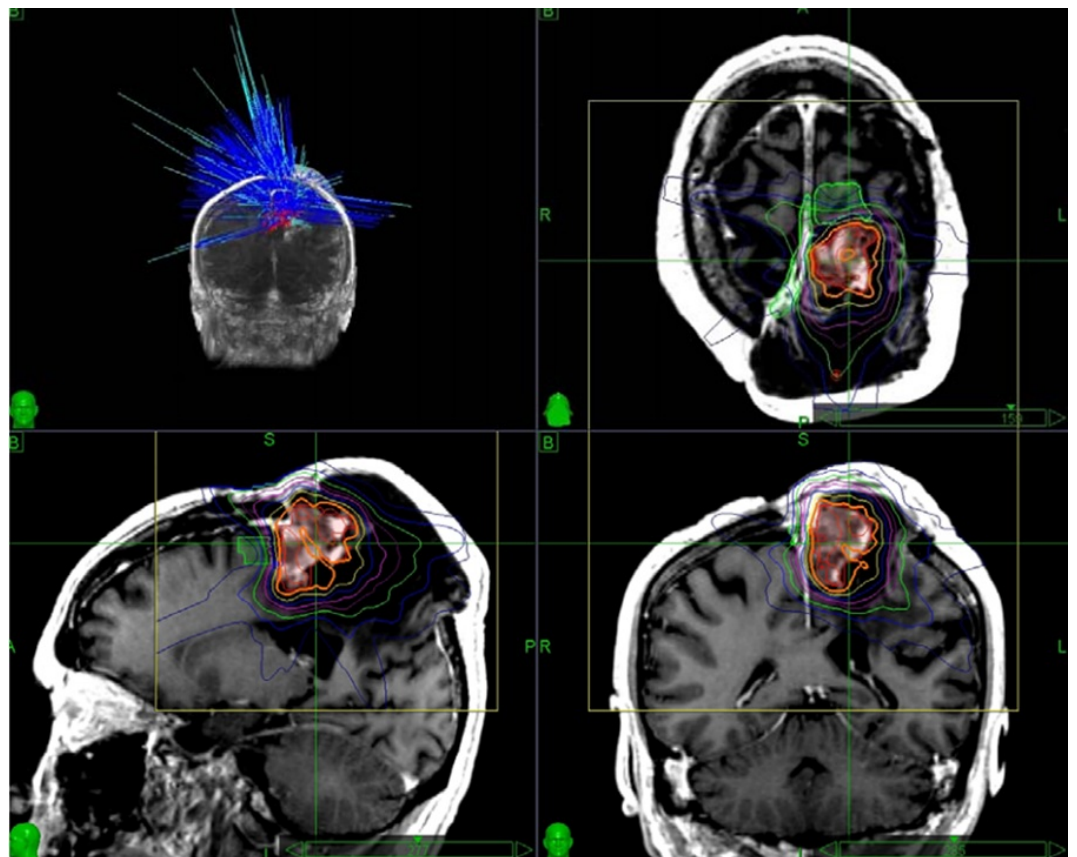
FIGURE 3: Recurrent GB involving the left motor cortex in a 56-year-old man seven months after exeresis complemented by administration of temozolamide and EBRT.

Single-stage CyberKnife radiosurgery delivering 21 Gy prescribed to the 80% isodose line (maximum dose: 26.2 Gy) was well tolerated and achieved growth control (>1 year).

Synchrotron-generated microbeams: a new tool for the treatment of GB

Synchrotron sources allow the delivery to the brain of highly collimated, quasi-parallel arrays of X-ray microplanar beams (microbeams). Microbeams produced by third generation synchrotron sources, such as the one at the European Synchrotron Radiation Facility (ESRF) in Grenoble, have a typical size of 25-100 1tm and median energy of 50-600 keV. Highly brilliant synchrotron sources, such as the ESRF, are characterized by an extremely high-dose rate associated with almost null beam divergence. The minimal beam divergence allows extremely steep dose gradients off the target and over the adjacent tissues, which thus receive doses in the order of two degrees of magnitude lower than the target dose. Safety and biologic efficacy of synchrotron-generated microbeams have been widely tested in several animal models, including mice, rats, piglets, and rabbits. Arrays of microscopic beams sized 25-100 p.m and separated by center-to-center distances 100-400 p.m have been used in most of the experiments, but wider submillimetric beams have been tested as well [9]. Peak entrance doses of several hundreds of Gy are surprisingly well-tolerated by normal tissues, up to tolerance of the vascular bed to microbeam irradiation [8].

Microbeam radiation therapy (MRT) has been tested in animal models of cancer, including primary brain tumors [9, 31-32]. Rats bearing implanted gliosarcoma showed a marked survival enhancement after microbeam irradiation [10]. In this study, the incident microbeam dose was 625 Gy, while size and spacing were respectively 25 and 200 p.m. Irradiated animals showed an increase in life span of 60.5%. Concomitant injection of a dose enhancer, such as gadolinium, increased survival even more dramatically, up to 131.6%. One out of six rats receiving microbeam irradiation after intratumoral gadolinium injection survived more than one year. Control non-irradiated rats with gliosarcoma displayed a median survival time of 19 days only. A study published in 1998 [33] evaluated three groups of 11-14 rats treated to one of three MRT regimens for 9L gliosarcoma: 625 Gy (skin-entrance) unidirectional, and 625 or 312.5 Gy cross-irradiated. Beam spacing was 100 p.m center-to-center with 25-11m wide beams. Untreated controls all died within 31 days. Greatest survival was in the 625-Gy bidirectional group, with 50% of the animals alive at day 115. Overall, more than half of the treated animals' tumors were completely ablated. Brain damage secondary to irradiation included "stripes" of cells with loss of nuclei/perikarya. A grid pattern was apparent in the cross-fired area.

Dilmanian, et al. [31] also inoculated rats with 9L gliosarcoma and treated them with several unidirectional MRT beam configurations and compared results with historical controls which had received broad-beam irradiation. Monte Carlo simulations of the dose distribution for this study indicated a valley dose range of -- 5-20% of the peak beam dose, depending on the beam spacing. This corresponded to a 100%-to-20% dose fall-off over less than 50 p.m and highlights the remarkably sharp edges achievable with low energy microbeams. Although the number of animals in each group was small, MRT was superior to results from historical broad-beam treated animals, and far superior to untreated controls: in the best group, 63% of animals survived 100 days post-tumor inoculation. Limited histological studies 398 days post-inoculation indicated tumor eradication in the majority of animals with modest amounts of radiation-induced brain damage.

MRT, like SRS, is a local treatment, and for this reason, its efficacy for GB may not differ from that for SRS. Nevertheless, the ability of synchrotron-generated microbeams to deliver much higher doses than conventional radiotherapy and SRS, while minimizing damage to normal tissues, supports strongly a potential role of microbeam radiosurgery in the treatment of malignant gliomas and GB. The technology must be carefully tested in Phase I clinical trials before its potential can be assessed [34-35].

Conclusions

Radiosurgery is an important treatment option for patients with high-grade gliomas. Radiosurgery is a non-invasive, well-tolerated treatment which can be combined with chemotherapy or other adjuvant treatments. In patients having an established diagnosis of high-grade glioma, recurrent disease can be effectively treated, even if conventional fractionated radiotherapy has been performed already. Preliminary investigations show an increased survival length in patients with residual or recurrent GB. CyberKnife radiosurgery is a particularly well-tolerated treatment due to the absence of the stereotactic frame, which can cause patient discomfort and restrict treatment beam delivery. The non-isocentric beam delivery capability of CyberKnife can offer enhanced conformality and homogeneity together with the ability to fractionate the treatments, if desirable. Excellent laboratory results for MRT also suggest a potential role for synchrotron-generated microbeams for the high-dose treatment of malignant brain tumors. All these features deserve further investigation with the hope to increase the survival, reduce side-effects, and improve the quality of life of patients diagnosed with GB.

Additional Information

Disclosures

Conflicts of interest: The authors have declared that no conflicts of interest exist.

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2012 Romanelli et al. Cureus 4(6): e48. DOI 10.7759/cureus.48

10 of 10