The Emerging Role of Stereotactic Radiosurgery in the Treatment of Glioblastoma Multiforme

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Abstract: Stereotactic radiosurgery is an emerging treatment option offered to patients with Glioblastoma multiforme (GBM). Radiosurgery is performed as an outpatient procedure and provides a safe and effective non-invasive treatment for focal GBM. High energy beams originating from cobalt sources placed into an helmet (Gamma-Knife) or generated by a linear accelerator (LINAC) rotating on a gantry (X-Knife, Novalis) or maneuvered by a robotic arm (CyberKnife) are delivered with submillimetric accuracy to a selected intracranial target. Treatment accuracy is provided by image-guided volumetric CT and MR studies complemented with advanced metabolic neuroimaging techniques such as CT-PET. Radiosurgery is typically used as a salvage treatment in patients with recurrent GBM to avoid further surgical procedures or as a complement to conventional fractionated radiotherapy. This paper reviews the emerging role of stereotactic radiosurgery in the treatment of GBM.

Keywords: Fractionated stereotactic radiotherapy, Glioblastoma multiforme, image-guidance, stereotactic radiosurgery.

INTRODUCTION

Glioblastoma Multiforme (GBM) is an intra-axial malignant brain tumor accounting for 2% of adult cancer deaths with an incidence of approximately 5 per 100,000 individuals per year in North America [1]. Current management of newly diagnosed GBM includes a combined approach of surgery, adjuvant concomitant fractionated irradiation and chemotherapy. Radical microsurgical resection remains the main step to provide to GBM patients an extended survival [2]. Further survival improvements are provided by subsequent chemotherapeutic agents, prognosis remains poor, with a 5 years survival ranging from 1.9% to 9.8% [3,4] and a striking rate of local recurrence [5,6]. Despite remarkable technological improvements affecting all aspects of the multimodal GBM management, treatment accuracy remains a major issue to improve survival. Several salvage approaches have been proposed over the last years, with radiosurgery emerging lately as a safe and effective way to manage loco-regional recurrent disease. While conventional fractionated radiotherapy has a clear role and a demonstrated efficacy as first line therapy [5], it’s rarely used to treat the almost inevitable recurrences in patients already irradiated due to the increased risk of radionecrosis. Radiosurgery in newly diagnosed GBM most commonly involves the delivery of a boost to the tumour bed following surgery and/or conventional external-beam radiation therapy (EBRT), but radiosurgery can also be employed as a primary treatment modality in patients harbouring small lesions (3 cm or less in diameter) and located in surgically inaccessible regions such as the thalamus, hypothalamus and basal ganglia or in patients that are too ill for surgical resection. More commonly, radiosurgery is offered to patients with focally recurrent disease due to its ability to effectively ablate the tumor volume, thereby avoiding the need for a second surgical approach. Image-guided radio-surgery provides an excellent non-invasive treatment option for GBM patients harbouring a focal recurrence: treatment is very short and does not sacrifice a vast amount of time in patients who already have a limited life expectancy. High doses can be delivered to the target within a very short time with thigh and conformal dosimetry sparing the adjacent tissues from radio-induced damage.

IMAGE-GUIDED STEREOTACTIC RADIOSURGERY (SRS)

The basic feature of SRS is the ability to deliver a high-dose of radiation to a selected intracranial target in a single session. The thigh spatial dose fall out provides a remarkable sparing of adjacent normal tissue. The delivery of high doses to the target with sparing of the adjacent brain is achieved through the use of multiple beams carrying minimal doses and converging in an isocentric or non-isocentric pattern over a selected volume. The overlap of over a hundred beams onto the target adds up to exceedingly high doses while the rest of brain tissue receives minimal doses. Conventional irradiation lacks the ability to spare adjacent brain and requires fractionated delivery to achieve biologically equivalent doses [6].

Single fraction high dose SRS is delivered typically in a very short time with enhanced radiobiological effect and can overcome GBM radioresistance affecting the tumor repopulation by dormant stem cells located in hypoxic and necrotic regions. SRS requires relatively small targets (up to 7 cm³) in order to achieve a tight fall off preserving the adjacent tissue from damage. The emergence of new radiosurgical frameless devices allows the combination of the radiosurgical approach...
with hypofractionation and safe treatment of larger tumor volumes [7].

Image-guidance is the basis for the precise delivery of a large number of radiant energy beams to an intracranial target. These beams can be painted over or crossfired through the target depending upon the treatment planning modalities of the device being used. The head of the patient is either held by a stereotactic frame affixed to the skull and providing a fixed position or contained by a thermoplastic mask allowing modest movements, which are detected and compensated in real time. These different treatment modalities are defined as frame-based and frameless radiosurgery. Until the introduction of CyberKnife in late ‘90s, radiosurgery was delivered only through frame-based techniques. The introduction of an image-guided robotic arm positioning a lightweight 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 body districts.

FRAME-BASED RADIOSURGERY

Radiosurgery was developed by Lars Leksell [8] as a technique delivering high energy beams to a selected intracranial target with overwhelming precision. Head fixation is an essential step: the patient’s head is fixed by a stereotactic frame providing the spatial tri-dimensional references needed to deliver the therapeutic beams with submillimetric accuracy. The current Gamma Knife System Perfexion (GKS) utilizes 192 individual cobalt-60 [60Co] gamma ray sources, placed within a helmet-like configuration. Collimator position and size are changed robotically. A stereotactic frame is required to immobilize the patient’s head and providing a fixed position or contained by a thermoplastic mask allowing modest movements, which are detected and compensated in real time. These different treatment modalities are defined as frame-based and frameless radiosurgery. Until the introduction of CyberKnife in late ‘90s, radiosurgery was delivered only through frame-based techniques. The introduction of an image-guided robotic arm positioning a lightweight 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 body districts.

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. This and other frame-based systems are typically used to treat intracranial targets with a single session, because wearing the frame for more than a few hours is not practical and can induce progressive localization error due to shifting of the pins fixing the frame to the skull. Frameless radiosurgery is based on real-time image guidance provided by digitally reconstructed skull radiographs [16,17]. Frameless radiosurgery is a novel treatment modality based on advanced image-guidance techniques providing accurate and precise beam delivery in the absence of a rigid frame. Frameless radiosurgery removes the need to apply an invasive frame to the patient’s skull and also enables the option of hypo-fractionation. The absence of a frame hanging parallel to the skull base opens the possibility to use a vast array of penetration trajectories through the visceral skull with consequent brain and related crucial structures sparing.

The CyberKnife is the most diffuse frameless radiosurgery device (Table 1). CyberKnife radiosurgery combines non-invasive image-guided localization and a robotic lightweight high-energy radiation source to deliver accurate and precise irradiation to any region of the body in one or multiple sessions. The treatment planning system of the CyberKnife exploits the robot’s 6-degree of freedom maneuverability allowing non-isocentric targeting that superimposes an overlapping array of up to 1600 beam trajectories on the target. An inverse planning procedure optimizes the set of beam directions and dose to be used, delivering homogeneous dose distributions closely conforming to highly irregular volumes. As a result the CyberKnife has submillimetric accuracy [18] and can be used to treat intracranial lesions (Figs. 1, 2) as well as extracranial spinal lesions including intramedullary AVMs [16,17,19] and lesions in the chest and abdomen [20].

The combination of sophisticated real-time image guidance techniques and robotic delivery is the basis of the CyberKnife’s precision and accuracy. 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
Table 1. Radiosurgical Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Source</th>
<th>Description</th>
<th>Frame</th>
<th>Extracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma knife (Elekta Stockholm, Sweden)</td>
<td>Gamma ray</td>
<td>Cobalt-60 source, isocentric beam ranging from 4 to 16 mm. The longest follow-up lesions in the brain SRS treatment</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CyberKnife (Accuray, Sunnyvale, CA)</td>
<td>X-ray, s-band/6 MV</td>
<td>Robotic radiation delivery with submillimetric accuracy in virtually any direction. Non isocentric planning. Collimator size: 5-60mm. Continuous image up-date</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Novalis (BrainLAB, Feldkirchen, Germany)</td>
<td>X-ray, s-band/6 MV</td>
<td>Standard Varian LINAC, 32 isocentric leaf pairs width 2.5mm, plus 14 pairs nonisocentric width 5mm. X-ray detector for reproducible set-up</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TomoTherapy HI-ART (Accuray, SUNnivale, CA)</td>
<td>X-ray, s-band/6 MV</td>
<td>Helical IMRT on CT mounted LINAC, 64-multileaf collimator, allowing 6.25-mm-wide beam</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3D-IMRT volumetric arc [Elekta (VMAT; Stockholm, Sweden) Varian (RapidArc; Palo Alto, CA)]</td>
<td>X-ray, s-band/6 MV</td>
<td>IMRT using 3D volumetric images applied to a volumetric arc delivery system</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Fig. (1). CyberKnife treatment planning delivered as the primary treatment option following stereotactic biopsy in a patient with hypothalamic GBM.

The robotic arm adjusts the pointing of the LINAC therapeutic beam to the target. In essence, the robotic arm can follow the changes in patient position by preserving the patterns at which the beams traverse patient 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 relatively 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 to the targeting structures (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 [21,22].
STEREOTACTIC RADIOSURGERY REGIMES FOR GBM

Several retrospective studies have investigated the role of SRS in the treatment of GBM both as part of the initial treatment or as salvage therapy in recurrence. In a recent meta-analysis performed by Panullo et al. [23] on the role of SRS in neuro-oncology with strict inclusion-exclusion criteria eleven studies were found falling under the class II and III of evidence. Between those the prospective randomized study by Souhami and co-workers [24] on behalf of the Radiation Therapy Oncology Group (RTOG) on the role of SRS in combination with carmustine (BCNU) on patients with newly diagnosed GBM failed to meet the criteria of a class I. The trial, indeed, was not blinded in outcome assessment and even though a cross-over between groups was not planned, several patients underwent salvage radiosurgery. The study data were unable to prove a survival benefit of SRS group median survival from irradiation (mos) of 13.5 months, whereas the control group had a median survival of 13.6 months. Anyway the authors didn’t analyze the role of SRS alone as a boost or in recurrent GBM, leaving uncovered this aspect other groups have tried to address such open questions [24-33].

In contrast with the result of Kondziolka and colleagues [25] which showed a better mos of 30 months for those treated at tumor progression compared with a global 26 months for the entire series, in the data recently presented by Biswas et al. [26] time of treatment didn’t have a prognostic significance in term of mos which was 6.7 months (range 1.4-74.7), also if the progression-free-survival was better for the group of patients receiving up-front SRS (6.0 versus 3.4 months).

Kong et al. [27] in their prospective cohort study treated 114 consecutive patients both with recurrent grade III and IV tumor obtaining respectively 37.5 months and 23 months of mos. Comparing results with a historic group they found a significant increase in survival although only in the GBM group without significant toxicity. The treatment was almost in all cases delivered with a GKS and the mean volume targeted was 10.6 ml, which can have a role in outcome. The first to identify positive prognostic factor in patients undergoing SRS was Shrive et al. [28], who found that age and gross tumor volume (GTV) inversely correlate with survival. Patient younger that 46 years old had a mos of 15.5 months compared with 8.2 months for the older ones and GTV less than 10.1 cm³ had a survival of 15.1 instead of 8.1 months for larger tumors.
Similar prognostic factors were confirmed by recent article published by Pouratian et al. [29] where age and clinical status were considered entering both the criteria for assigning patients to the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification. Class III patients (those with extensive surgical resection and not on steroids at the time of radiation) had a significantly improved overall survival (OS) of 34.5 months. Extent of surgical resection significantly affected survival, also in the data presented by Villavicencio and colleagues [30], where patients who underwent biopsy did worse than those in which gross removal was attempt. In this retrospective multicentric study designed to assess eventually the role of SRS delivered by CyberKnife for GBM also in newly diagnosed GMB patients compared with recurrences, the authors didn’t demonstrated a survival benefit for the first group which had a mos of 11.5 months against 24 months for the recurrent GBM group. No significant correlation was found in treatment CyberKnife parameters, RPA classes, treatment time and volumes.

For what concerns the toxicity of re-irradiation with an SRS approach, according to the article published by Hall et al. [31], patients harbouring large recurrent grade III and IV gliomas (mean GTV of 20 cm³) experienced a relative high rate of severe side-effects, with a 33% of them requiring re-operation for increased intracranial pressure due to radio-induced necrosis mass effect. In other series, despite a general low profile of side-effects, as in Biswas et al. series [26], the risk of additional surgery is present. Unacceptable re-operation rate due to radio-induced necrosis ranging from 10 to 31% were reported also in other studies [32,33], although the causes where not clearly identified raising potential suspicion concerning higher median delivered dose and larger GTV.

FUNCTIONAL AND METABOLIC IMAGE FUSION FOR SRS TREATMENTS

Failure of efficacy of additional radiation therapy is often due to tumor progression close to the treated target or because of unsuccessful identification of distant pattern of recurrence. Different studies above cited have reported that in re-operated patients often pathological analysis demonstrated an infiltration of glial tumor cells in the contest of radio-induced necrosis [26,31].

Early recognition can allow treatment of smaller volume lesions with an improvement in survival and lower side-effects profile. Close follow-up of patients with GBM is routinely done with MRI, but standard diagnostic sequences should be today integrated by specific protocols. Simple T1-weighted contrast enhanced sequence relaying on the blood-brain barrier damage, is sometimes unable to localize the spreading patterns of glioma cells. On the other hand T2-weighted sequences often overestimate the tumor volume due to the confounding signal of edema [42].

Nowadays neuro-imaging of glioma should be completed with metabolic and functional information coming out from an integration of different technologies including nuclear medicine devices such as CT-PET scanner. Metabolic studies have the aim to identify specifically the activity of tumor cells with high specificity and sensibility. This is really important especially in the contest of recurrent high grade gliomas, where artifacts generated by previous treatment i.e. surgery, conventional radiation therapy or chemotherapy can bring clinicians to ambiguous and misleading results.

Proton MR-spectroscopy is a non-invasive technique to investigate metabolic changes in brain lesions. Although no tumor-specific metabolites have been identified so far, specific patterns of metabolites changes normally present in brain (choline, N-acetylaspartate, creatinine, lactate) and their concentration can give a precise view of tumor activity [43]. Proton-emission tomography (PET) is a device which truly investigates metabolites of tumor cells, injecting radiolabeled tracers is it able to localize their accumulation in pathologic cells. CT-PET has the capability of coupling metabolic and CT anatomical images, generating the more precise spatial resolution needed for surgical and radiosurgi-
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The most diffusely used tracer in neuro-oncology is the $^{18}$F-fluorodeoxy-glucose (FDG), but others have been recently introduced linked to aminoacid metabolism: $^{11}$C-methionine (11C-MET), 6-$^{18}$F-fluoro-L-Dopa ($^{18}$F-FDOPA), 3-deoxy-3-$^{18}$F-fluoro-L-thymidine ($^{18}$F-FLT) [44-46].

Functional MRI (fMRI) is a radiological technique able to localize brain functions non-invasively, as sensory or motor functions, language and memory. This can give useful information in case of recurrent gliomas close to eloquent areas. Diffusion tensor imaging (DTI) is an MRI technique used to identify the orientational properties of the diffusion process of water molecules in biological tissues. These data are processed to identify integrity of white matter fibers, rebuilding the trajectories, for example of cortico-spinal fasciculus or optic pathway, leading to the formation of in vivo and individualized white matter map. In the case of brain tumors, DTI, and fiber tractography, allows assessing the anatomical relationship between the lesion and white matter tracts and helps discrimination between displacement and infiltration of highly relevant white matter tracts [47-50].

A precise definition of the target is fundamental for a tailored radiosurgical treatment. All data coming from neuroimaging studies can be fully integrated in image-guided software of radiosurgical devices. The fusion between high resolution anatomical volumetric MRI, metabolic CT-PET images and functional MRI is a complex procedure that requires time, specific knowledge and further optimization, but it will significantly improve SRS outcome.

CONCLUSION
SRS and fSRT are feasible and safe non-invasive treatments for GBM patients (Table 2). Retrospective studies have suggested a survival benefit in younger patients with a good clinical status and smaller tumors [28,29]. An advent in terms of survival has been inconstantly demonstrated in recurrent GBM compared to up-front therapy for newly diagnosed tumors [30,31]. However to make a final conclusion larger prospective trials are needed, since retrospective studies may have selection bias [23].

CONFLICT OF INTEREST
The author(s) confirm that this article content has no conflicts of interest.

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Declared none.

Table 2. Published Studies on Patient Treated with SRS and fSRT for High Grade Glioma, (mos = median survival from irradiation; OS = overall survival; Reop. rate = reoperation rate)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Ref</th>
<th>Device</th>
<th>Grade</th>
<th>n</th>
<th>Recurrent</th>
<th>Median dose (Gy)</th>
<th>Fraction</th>
<th>Median tumor size (GTV) cm$^3$</th>
<th>Mos (months)</th>
<th>OS (months)</th>
<th>Reop. rate (%)</th>
</tr>
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<tbody>
<tr>
<td>Pouratian</td>
<td>2009</td>
<td>29</td>
<td>GK</td>
<td>IV</td>
<td>48</td>
<td>26</td>
<td>6 (3-15)</td>
<td>1</td>
<td>21.3 (0.3–110.0)</td>
<td>9.4</td>
<td>16.25</td>
<td>0</td>
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<tr>
<td>Villavicencio</td>
<td>2009</td>
<td>30</td>
<td>CK</td>
<td>IV</td>
<td>46</td>
<td>26</td>
<td>26.7 (11.4-36.9)</td>
<td>1</td>
<td>7 (0.4-48.5)</td>
<td>9.5/7*</td>
<td>11.5/21*</td>
<td>NA</td>
</tr>
<tr>
<td>Patel</td>
<td>2009</td>
<td>36</td>
<td>LINAC</td>
<td>IV</td>
<td>26</td>
<td>26</td>
<td>18 (12-20)</td>
<td>1</td>
<td>10.4 (0.3–60.1)</td>
<td>8.4</td>
<td>24.4</td>
<td>11</td>
</tr>
<tr>
<td>Patel</td>
<td>2009</td>
<td>36</td>
<td>LINAC</td>
<td>IV</td>
<td>10</td>
<td>10</td>
<td>36</td>
<td>6</td>
<td>51.1 (16.1-123.3)</td>
<td>7.5</td>
<td>24.1</td>
<td>10</td>
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<td>2009</td>
<td>26</td>
<td>Novalis</td>
<td>IV</td>
<td>33</td>
<td>18</td>
<td>14 (6-20)</td>
<td>1</td>
<td>9.2 (0.2-85.4)</td>
<td>6.7</td>
<td>16.9</td>
<td>3</td>
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<td>Fokas</td>
<td>2009</td>
<td>39</td>
<td>LINAC</td>
<td>IV</td>
<td>53</td>
<td>53</td>
<td>30 (20-60)</td>
<td>5-12</td>
<td>35.01 (3-204)</td>
<td>9</td>
<td>27</td>
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<td>2008</td>
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<td>LINAC</td>
<td>IV</td>
<td>114</td>
<td>114</td>
<td>16 (12-50)</td>
<td>1</td>
<td>10.6 (0.09–79.6)</td>
<td>13(IV), 26(III)</td>
<td>23(IV),37, 5(III)</td>
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<td>Ernst-Stecken</td>
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<td>40</td>
<td>Novalis</td>
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<td>11</td>
<td>11</td>
<td>35</td>
<td>7</td>
<td>5.75 (0.77-21.94)</td>
<td>18 (28%)</td>
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<td>LINAC</td>
<td>IV</td>
<td>32</td>
<td>32</td>
<td>15 (10-20)</td>
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<td>10 (1.2–59.2)</td>
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<td>53</td>
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<td>15-31</td>
<td>49.3 (2.5-636)</td>
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<td>Cho</td>
<td>1999</td>
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<td>LINAC</td>
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<td>46</td>
<td>46</td>
<td>17 (9-40)</td>
<td>1</td>
<td>10 (1-54)</td>
<td>11</td>
<td>NA</td>
<td>22</td>
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<td>Cho</td>
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<td>15</td>
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<td>6.4 (0.3-96)</td>
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<td>IV,III</td>
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REFERENCES


