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Assessment of Volumetric Modulated Arc Therapy in Management of High grade Glioma

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Abstract: High-grade gliomas (HGGs), which include glioblastoma (GBM) and anaplastic astrocytoma (AA), are the most common intrinsic brain tumors in adults and are nearly uniformly fatal. The age-adjusted annual incidence of histologic verified glioma was 7.3 cases per. 100,000 person-years. High-grade gliomas were present in 85%. There have been significant advances in the delivery of radiotherapy over the past few decades. These include increased sophistication of imaging techniques, which has resulted in improved accuracy of target volume definition and delineation, as well as developments in treatment planning systems and linear accelerator delivery capabilities leading to improved dose distributions and conformity. These developments have been mainly driven by the need to reduce the dose to normal tissue structures and thereby minimise the risk of toxicity and morbidity, which then allows dose escalation to the tumour volume potentially leading to improved locoregional control. To that end, newer radiation techniques, e.g. intensity modulated radiotherapy (IMRT), have been developed. IMRT techniques employ variable intensity across multiple radiation beams leading to the construction of highly conformal dose distributions. This is achieved by subdividing each radiation beam into smaller radiation beamlets and varying the individual intensities of these beamlets. The advantages of this technique are improved target volume conformity, particularly in volumes with complex concave shapes, and improved sparing of normal tissues and organs at risk (OARs) resulting in reduced acute and late toxicities

Keywords: *Volumetric Modulated Arc Therapy, High grade Glioma*

Introduction

Gliomas are the most common primary malignant brain tumors. They account for 80% of all malignant primary brain and central nervous system tumors, with an annual age-adjusted incidence of 5.55 per 100,000 in the United States [1].

In general, gliomas are classified into four grades based on histology: grades I and II are considered low-grade gliomas, and grades III and IV are considered high-grade gliomas. Grade III gliomas include anaplastic astrocytomas that are classified based on mutations in the isocitrate dehydrogenase (IDH) gene into IDH-

mutant, IDH-wildtype, and not otherwise specified (NOS) categories; anaplastic oligodendrogliomas that are diagnosed on the basis of combined whole arm losses of chromosomes 1p and 19q (1p/19q codeletion) in addition to IDH mutation; and anaplastic oligodendrogliomas NOS (absence of both 1p/19q codeletion and IDH mutation) [2].

Grade IV gliomas include glioblastoma, IDH-wild type (approximately 90% of cases); glioblastoma, IDHmutant; and glioblastoma, NOS. For more information on tumor classification, refer to the article ‘‘2016 World Health Organization Classification of Central Nervous System Tumors’’ by Patrick Y. Wen, MD, FAAN, and Jason T. Huse, MD, PhD, in this issue of Continuum [3].

There have been significant advances in the delivery of radiotherapy over the past few decades. These include increased sophistication of imaging techniques, which has resulted in improved accuracy of target volume definition and delineation, as well as developments in treatment planning systems and linear accelerator delivery capabilities leading to improved dose distributions and conformity. These developments have been mainly driven by the need to reduce the dose to normal tissue structures and thereby minimise the risk of toxicity and morbidity, which then allows dose escalation to the tumour volume potentially leading to improved locoregional control [4].

To that end, newer radiation techniques, e.g. intensity modulated radiotherapy (IMRT), have been developed. IMRT techniques employ variable intensity across multiple radiation beams leading to the construction of highly conformal dose distributions. This is achieved by subdividing each radiation beam into smaller radiation beamlets and varying the individual intensities of these beamlets. The advantages of this technique are improved target volume conformity, particularly in volumes with complex concave shapes, and improved sparing of normal tissues and organs at risk (OARs) resulting in reduced acute and late toxicities [5].

IMRT also has the ability to produce inhomogeneous dose distributions, which allows the simultaneous delivery of different doses per fraction to separate areas within the target volume. This could facilitate localised dose escalation strategies without increasing total treatment time (for example, by using hypofractionated regimens), which may have the potential radiobiological benefit of reducing the impact of accelerated repopulation in tumour clonogens [6].

Despite the obvious benefits of IMRT, there are still some disadvantages. The planning and quality assurance (QA) processes required for IMRT are more complex and time-consuming compared with conventional conformal radiotherapy (CRT) techniques, which can have significant impact on departmental resources. However, several commercial systems are now available that allow multiple plan measurement of IMRT plans and facilitate batching of patient QA measurements to improve efficiency [7].

A standard IMRT plan often requires multiple fixed angle radiation beams, which can increase treatment delivery time. This can impact on patient comfort on the treatment couch, reproducibility of treatment position and intrafraction motion. There are also some concerns that the increased treatment time could have radiobiological implications owing to the possibility of increased tumour cell repair and repopulation during the extra time required to deliver the treatment [8].

IMRT plans use a larger number of monitor units (MU) compared with conventional CRT plans leading to an increase in the amount of low dose radiation to the rest of the body. The number of MU used in fixed field IMRT depends, to some degree, on the IMRT technique; usually more MU are required in the sliding window (SW) or dynamic IMRT technique. In this technique, each radiation beam is modulated by continuously moving multileaf collimators (MLCs). This is in contrast to the step-and-shoot (SS) or static techniques in which each beam is subdivided into multiple segments with differing MLC shapes and the beam is switched off between segments [9].

The increase in MU and subsequent increase in low dose radiation has led to concerns of increased risk of secondary radiation-induced malignancies, which is of particular relevance in paediatric patients or patients with long life expectancies. There are estimates in the literature that the number of MU in an IMRT plan is two

to three times higher than a conventional radiotherapy plan with an increase in the incidence of radiation-induced secondary malignancies from 1−1.75% for patients who survive for 10 years or more [10].
There has been some interest in arc-based or rotational therapies in an attempt to overcome some of the limitations associated with fixed field IMRT. The basic concept of arc therapy is the delivery of radiation from a continuous rotation of the radiation source and allows the patient to be treated from a full 360° beam angle. Arc therapies have the ability to achieve highly conformal dose distributions and are essentially an alternative form of IMRT. However, a major advantage over fixed gantry IMRT is the improvement in treatment delivery efficiency as a result of the reduction in treatment delivery time and the reduction in MU usage with subsequent reduction of integral radiation dose to the rest of the body [11].
In addition to the subsequent advantages from the shorter treatment delivery time, a further potential benefit is the availability of extra time within a set treatment appointment time slot to employ image-guided radiotherapy (IGRT). IGRT involves the incorporation of imaging before and/or during treatment to enable more precise verification of treatment delivery and allow for adaptive strategies to improve the accuracy of treatment. The main drawback of IGRT is the requirement for more time on the treatment couch and an increase in the total amount of radiation to the patient, especially with daily IGRT imaging schedules. These disadvantages are less of an issue with arc therapies, which have shorter treatment delivery times and fewer MU [12].
There are two main forms of arc-based therapies: tomotherapy and volumetric modulated arc therapy (VMAT). Tomotherapy (i.e. “slice therapy”) machines can be considered to be a combination of a CT scanner and a linear accelerator that can deliver the radiation in a fan-shaped distribution, similar to CT imaging with a continuously rotating radiation source, while the patient is moved through the machine. Tomotherapy techniques can be subdivided into axial or serial tomotherapy (where the radiation is delivered slice by slice) or helical tomotherapy (HT) (where the radiation is delivered in a continuous spiral). There is limited data on axial tomotherapy in comparison with fixed field IMRT. HT has been evaluated in a variety of tumour sites and it can generally achieve either similar or improved dose distributions compared with fixed field IMRT, with variable results on treatment time comparisons [13].
VMAT was first introduced in 2007 and described as a novel radiation technique that allowed the simultaneous variation of three parameters during treatment delivery, i.e. gantry rotation speed, treatment aperture shape via movement of MLC leaves and dose rate. The earlier form of arc therapy, termed intensity modulated arc therapy (IMAT) was first described in 1995 and required the use of multiple superimposed arcs to achieve a satisfactory dose distribution. More recent VMAT techniques have allowed the whole target volume to be treated using one or two arcs, although complex cases may require more. In a recent review, VMAT is essentially described as a form of single arc IMAT technique that employs dose rate variation [14].
One benefit of VMAT compared with tomotherapy is the possibility of delivering this treatment on conventional linear accelerators, which are configured to have this capability. Currently there are several VMAT systems available under various names (RapidArc, Varian; SmartArc, Phillips; and Elekta VMAT, Elekta) [15].
IMRT vs VMAT
A study in 2017 of patients treated with SIB-IMRT and SIB-VMAT to the whole pelvis recorded no significant difference in the rate of acute genitourinary (GU) or gastrointestinal (GI) toxicities and no reported late Grade III toxicity of GI and GU except for rectal toxicity between the two groups. The recommendation was therefore that dose escalation using SIB-IMRT or VMAT with daily CBCT will reduce radiation toxicity to the bladder and rectum [16].
A year later, Tondel et al studied the use of daily CBCT vs weekly orthogonal images on a 250 patient cohort receiving 3DCRT using field-in-field technique. Though Tøndel observed daily CBCT verification significantly reduced rectal irradiation, this gain was not translated into a reduction of acute side-effects. A similar study as Tøndel using VMAT may produce more promising clinical outcomes [17].

Randomized clinical outcome studies are emerging for locally advanced high-risk carcinoma of the prostate and conclude prostate and pelvic lymph node IMRT is safe. Although higher Grade II toxicities are observed when compared with prostate only studies low levels of GI and GU toxicity scores from physician and patient reported assessments were achieved 24 months after treatment. Whilst regional nodal irradiation provides a survival advantage to patients with localized high-risk breast cancer; studies have not concluded whether the same effect is seen in prostate cancer [17].

Owing to the time and financial implications of randomised clinical outcome studies, currently the literature has described IMRT findings more than VMAT. However, VMAT has been used to assess fractionation and image guidance implying that it has been widely adopted as the gold-standard for prostate radiotherapy [18].

Glioblastoma multiforme (GBM)

Published literature has illustrated the dosimetric and efficiency advantages of VMAT to IMRT for GBM management in treatment time reduction, dose reduction to the brain stem, hippocampi, optic chiasm and cochleae and improved target coverage and conformity, therefore explaining the increased implementation of VMAT over IMRT without clinical outcome data. Sheu et al was the first to assess the clinical benefit of VMAT for GBM and deduce if dosimetric advantages translated to clinical outcomes. Toxicity was assessed and recorded weekly and an MRI with contrast taken 1-month post-RT [19].

No significant difference was observed in median OS (18.4 months IMRT vs 22 months VMAT: $p = 0.33$) and dermatological toxicities (81% alopecia; 58% erythema); however, fatigue (57%) and headaches (20%) were reported by both groups with no difference in toxicity incidence as well. Sheu et al concluded that care should be used in correlating dosimetric gain to clinical effects and centres should understand new techniques before adoption [20].

Another study assessed the impact of chemoradiation using VMAT on survival and disease progression or tumour failure at the contralateral hippocampus (cHC) for 82 patients with GBM over 4 years (2014–2018). The median follow-up for survivors was 11.7 months (range, 3.6–39.1) with a median OS of 23.5 months (95% CI: 18.4–28.7 months) and median PFS of 9.7 months (95% CI, 7.9–11.5 months). 6- and 12-month cHC failure-free rates were high at 98.7 and 97.2% respectively and overall tumour-failure at the cHC was low with 7.3% observed at the cHC and 9.8% failure observed at a 1-cm margin to the cHC [21].

Wee et al therefore concluded that chemoradiation using HA-VMAT produced low incidence of cHC- and cHC + 1 cm-failure, and therefore can be safe in newly diagnosed cases of GBM once this technique does not impair target coverage [22].

Although there are several dosimetric studies of the potential impact of proton therapy for GBM, a recent publication observed that although the radiation exposure to normal tissue responsible for cognitive function was significantly less with proton therapy this did not translate to improved cognitive outcomes [23].

Brainstem gliomas

Brainstem gliomas though rare (approximately 2% of adult gliomas) occur more in younger adults, and hence must be studied when evaluating the suitability of radiotherapy during pregnancy. Brainstem gliomas are associated with high maternal mortality, therefore treatment with surgery or radiotherapy should not be delayed. Despite the high mortality, Rosen et al observed some favourable pregnancy outcomes and, concluded that the most optimum treatment plan can be determined through in vivo monitoring and phantom estimation studies [24].

Malignant glioma

For malignant gliomas, IMRT has been evaluated with several planning studies showing a dosimetric superiority for non-coplanar IMRT techniques compared with conventional 3D-CRT. Malignant gliomas are widely infiltrative in their extension with indistinct tumour margins that are difficult to accurately define. There is therefore a concern of increased risk of insufficient dosage of the target volume, especially with the steep dose gradients in IMRT plans. However, with more sophisticated imaging modalities to guide definition

of tumour margins, the ability to co-register diagnostic MRI with planning CT images for improved accuracy of target volume delineation as well as the potential benefit of improved OAR sparing and facilitation of dose escalation, IMRT should be considered as a potentially useful technique for the treatment of these often aggressive tumours [25].

Wagner et al conducted a planning study of 14 patients with malignant glioma (World Health Organization (WHO) Grade 3 or 4) comparing single arc VMAT with 5–9 field fixed field IMRT (SW) and 3D-CRT. Conformity was higher for VMAT and IMRT compared with 3D-CRT; VMAT performed slightly better than IMRT in this respect. However, PTV coverage (which in this study was calculated as the ratio of target volume covered by the 95% isodose line divided by the PTV volume) was superior in IMRT compared with VMAT (94.7% vs 90.5%). For PTVs that were distant to OARs, 3D-CRT performed as well as IMRT in terms of PTV coverage, but was significantly inferior to both IMRT and VMAT for PTVs that were situated close to OARs. Regarding OAR sparing, VMAT achieved slightly better sparing compared with the other two techniques. The volume of healthy tissue receiving low dose radiation (V5 Gy) and mean dose of healthy brain was the highest in VMAT plans and lowest in 3D-CRT plans (mean dose 27.9 Gy vs 25.8 Gy) [26].

Another study by Shaffer et al evaluated VMAT in 10 patients with WHO Grade 3 or 4 glioma and compared the VMAT plans with 7-field fixed field IMRT (SW). The authors attempted to reduce bias in their study by cross-planning between two experienced planners, each generating five new IMRT and VMAT plans to avoid systematic planner bias. The patient datasets were also selected to include only cases where the PTV overlapped with at least one OAR therefore increasing the difficulty and complexity of planning. The results essentially showed equivalence in PTV coverage, conformity and homogeneity between the two techniques. For OAR sparing, VMAT and IMRT achieved similar sparing of midline OARs (brainstem and optic chiasm), but VMAT was better at sparing peripheral OARs with a lower mean dose to the retina, optic nerve and lens [27].

Similar to Wagner et al's study, the mean dose to normal brain was significantly higher in the VMAT plans (by 12%) compared with IMRT [26].

While it is difficult to make definite conclusions from these planning studies, owing to their limitations, some recommendations have been discussed. Wagner et al suggest, for PTVs situated distant to OARs, 3D-CRT can achieve comparable and acceptable PTV coverage with better sparing of healthy brain and normal tissue and therefore would be the technique of choice. However, for PTVs close to OARs, either IMRT or VMAT would be preferable depending on the adequacy of PTV coverage, while bearing in mind the added benefit of reduced MU and treatment time with VMAT. Therefore, the preferred radiation technique for these tumours should be selected on an individual case basis and in certain situations IMRT or VMAT may not always offer the optimal solution [26]. Regarding the issue of increased radiation to healthy brain tissue, Shaffer et al postulate that this could possibly be reduced by setting constraints for normal brain in the optimisation process or using multiple, partial and/or non-coplanar arcs to avoid entry and exit beams through critical normal tissue structures [27].An example of dose distributions achieved with VMAT and fixed field IMRT for malignant glioma is illustrated in Figure 3.

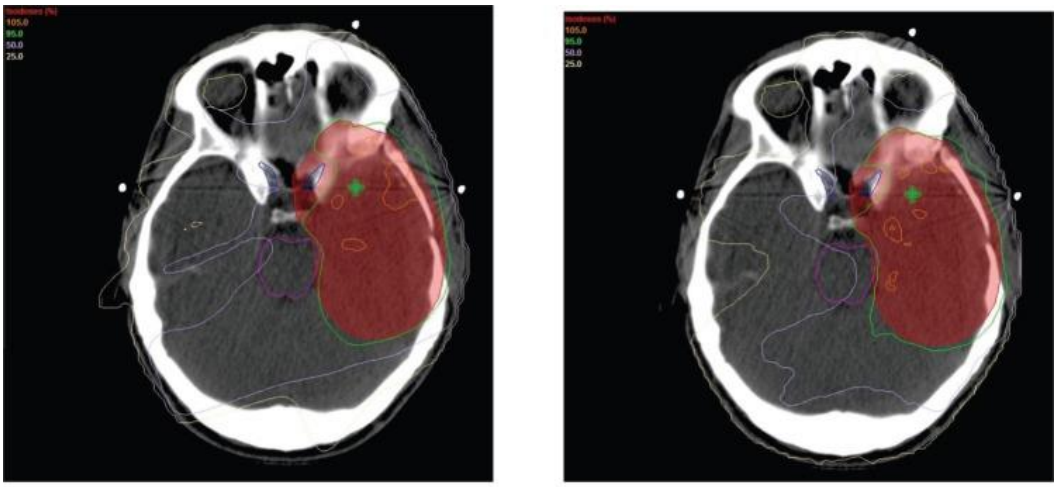

Figure 3 Example of dose distributions in (a) IMRT and (b) VMAT plans for malignant glioma. The dose prescribed to the planning target volume (PTV) (red contour) is 60 Gy in 30 fractions. The 95% isodose (green line) is encompassing most of the PTV. There is compromise of PTV coverage to allow sparing of the optic nerves (dark blue contour) and brain stem (pink contour) [27].

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