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*Review*

# Technical Advances in Radiation Therapy for Brain Tumors

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**Abstract.** *Radiation therapy plays a critical role in the management of brain tumors. Recent advances in radiation techniques include the use of intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) and stereotactic radiosurgery (SRS). All of these techniques allow the delivery of higher radiation doses to the target volume, at the same time reducing the risk of toxicity to normal tissues as compared with conventional 3D conformal radiotherapy (3D-CRT). Proton therapy may represent a treatment alternative to photon irradiation, due to the more favorable dose distribution to the target volume. This review summarizes current developments in radiation therapy and their clinical impact on the management of patients with brain tumors.*

Radiation therapy plays a critical role in the management of primary and secondary brain tumors. In the past few decades, radiotherapy (RT) has seen technical advances in all aspects of treatment, with improvement in patient immobilization, imaging, treatment planning and delivery. Advances in imaging and RT technology have enabled more precise tumor localization and dose delivery, leading to a reduction in the volume of normal brain tissue irradiated at high radiation doses. The principal aim of normal tissue sparing is to reduce the potential long-term toxicity of RT while maintaining its effectiveness. Radiation techniques have evolved from 3D conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic techniques, including either stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT). A further improvement in accuracy of radiation delivery has been made with the development of image-guided radiation therapy (IGRT), in which image guidance enables better precision in patient setup and target localization, allowing reduction of planning margins and leading to a smaller volume of healthy tissue irradiated at high doses. Currently, there is interest in the use of particle therapy for treating brain tumors because of the ability to concentrate the dose of protons and ions in the target volume while simultaneously sparing surrounding healthy tissues.

We provide a short review to summarize recent technical advances for irradiation of brain tumors, as well as highlight the potential benefits in terms of tumor control and reduction of long-term toxicity of different radiotherapy techniques.

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## IMRT and VMAT

Intensity-modulated radiation therapy represents the main evolution of 3D-CRT, in that it allows a superior dose distribution to the target volume and the delivery of highly conformal irradiation to concave and irregularly shaped volumes (1). Unlike conventional RT, the intensity of the radiation beams is delivered as a sequence of many small beams modulated by a multi-leaf collimator (MLC) in a dynamic sweeping manner (sliding window) or in a step-and-shoot manner, by using sophisticated computerized optimization planning (inverse planning). In clinical practice, the radiation oncologist delineates the target volume and specifies the prescribed radiation dose to the target and organs at risk (OARs). Based on these parameters, computer software optimizes the motion trajectories or segment shapes of the MLC to achieve intensity modulation, with the aim of improving dose conformity to the target while minimizing radiation exposure to surrounding normal tissue and OARs. In addition, the IMRT technique can be used to deliver different doses of radiation to different target volumes in a single phase as simultaneous integrated boost. Tomotherapy is a rotational form of IMRT in which dose conformity to the tumor is achieved by modulating the intensity of a rotating fan beam using MLCs (2). During treatment delivery, the patient is moved through the bore of the machine, while the gantry simultaneously rotates around him. A further evolution of IMRT technique is represented by VMAT, in which the radiation dose is continuously delivered as the gantry of the linear accelerator (LINAC) rotates around the patient through single or multiple arcs (3). VMAT provides a highly conformal dose distribution to the tumor, by modulating the intensity of the radiation beam, the dose rate and the gantry rotation speed, while shortening the treatment time and reducing the number of monitor units delivered, compared to conventional IMRT.

A recent advance in photon irradiation is represented by a new generation of LINAC with flattening filter (FF)-free beams (4). The removal of the FF allows an increase in dose rate up to four times compared to traditional FF beams. Therefore, the consequently shorter time of delivery can potentially reduce errors and obtain higher treatment accuracy, at the same time improving patient comfort.

The increased conformality achieved with IMRT and VMAT techniques may allow escalated tumor doses or hypofractionated radiation schedules without increasing toxicity to normal tissue, and thus may improve local tumor control and survival.

IMRT and VMAT are increasingly used for hippocampal sparing in patients undergoing brain irradiation for primary and secondary brain tumors, with the aim of avoiding long-term worsening of neurocognitive function (5). In patients with medulloblastoma, treatment with IMRT can achieve a lower rate of hearing loss and neurocognitive decline as compared with 3D-CRT (6-8). When used for either low-grade or high-grade gliomas, IMRT and VMAT allow for improved target conformity and better critical tissue sparing, including the hippocampus and brainstem; this might result in reduced late toxicities associated with RT. While the dosimetric superiority of IMRT and VMAT over 3DCRT for brain tumors has been clearly demonstrated for different tumor types (9-10), randomized studies are needed to assess the clinical advantages of these techniques in terms of efficacy and reduction of radiation-induced late toxicities. Concerns have been raised regarding the risk of secondary malignancies, due to higher integral dose to the surrounding healthy tissue with these modern techniques, especially for patients with long life expectancy (11). The estimated incidence of the risk for secondary cancer using IMRT for brain tumor treatment is approximately 130/10,000 persons/year (12). Longer follow-up and larger series are needed to report the real risk of late effects and clinical outcomes for IMRT and VMAT techniques.

## Stereotactic RT

Stereotactic irradiation represents a further refinement of CRT, with the advantage of improved patient immobilization achieved with the use of either a frame-based or a frameless mask stereotactic system, leading to submillimetric accuracy of patient repositioning. The radiation dose can be delivered as single-fraction, multi-fraction SRS (2-5 fractions), or as FSRT when conventional fractionation of 1.8-2.0 Gy per fraction is used. The main advantage of SRS is the ability to deliver a highly localized irradiation, as compared to conventional RT, leading to a reduction of the volume of normal brain tissue irradiated at high radiation doses, and minimizing the risk of the long-term consequences of treatment (13).

SRS can be delivered with the use of either a cobalt-60 gamma radiation-emitting source (Gamma Knife™; Elekta Inc., Stockholm, Sweden) or a LINAC. In its most used form, the Gamma Knife contains 201 small cobalt-60 sources of gamma rays arrayed in a hemisphere within a thickly shielded structure. A primary collimator aims the radiation emitted by these sources to a common focal point. A second external collimator helmet, which fits within the primary collimator, has an array of removable tungsten collimators (one per source) with circular apertures from 4-18 mm in size. For large and complex-shaped tumors, multiple radiation spheres can be used to cover the entire target in a multiple isocenter technique. The best tumor conformality is achieved by a different combination of number, size and position of the collimators. The dose is typically prescribed at 50% to obtain the maximum dose at the center of each pinpointed target and minimal dose at the target edge. In LINAC SRS, the dose is delivered with the use of multiple arcs or beams resulting in a similar high dose differential between the target and normal brain tissue. Isodose gradients can be improved using intensity modulation of the beams, restriction of gantry angles and arc lengths, microcollimation, and multiple-isocenter plans. The use of VMAT for SRS with FF-free LINACs allows reduction of overall treatment time, as compared with delivery using conventional FF beams (14). CyberKnife (Accuray, Sunnyvale, CA, USA) is a relatively new technological device which combines a mobile miniaturized LINAC mounted on a robotic 6-degree-of-freedom treatment arm, with an image-guided robotic system. Patients are fixed in a thermoplastic mask and the system allows for either single-fraction or multi-fraction SRS achieving the same level of targeting precision as for frame-based SRS.

SRS is frequently employed to treat both malignant and benign brain tumors and, regardless of the superiority claimed for each of these techniques in terms of dose homogeneity and conformality, the reported clinical efficacy and toxicity are similar (15). The role of SRS in the management of brain metastases is rapidly evolving, and SRS has been widely adopted as an alternative to whole-brain radiotherapy to treat patients with up to 10 brain metastases, with the aim of reducing the risk of neurocognitive impairment (16, 17). LINAC-based SRS is usually performed using a single isocenter to treat each lesion. Recently, the use of a single-isocenter technique for the simultaneous treatment of multiple brain metastases, in a single or few sessions, has been evaluated. Preliminary results are promising, showing an improvement in the efficiency of the delivery, while reducing overall treatment time and maintaining a high local control rate (18). SRS or hypofractionated stereotactic RT alone or in association with chemotherapy have been used as salvage therapy for patients with recurrent or progressive malignant gliomas, with a reported median survival of 6-11 months (19,20). For patients with benign brain tumors, including meningiomas, pituitary adenomas, craniopharyngiomas, and acoustic neuromas, local control after either SRS or FSRT is in the range of 80-95% at 5-10 years, with a low incidence of long-term toxicity (21-24).

## IGRT

Radiation delivery with IMRT or VMAT allows a steep gradient between the target volume and surrounding tissues obtaining a dosimetric benefit. Accurate image guidance is required during delivery of radiation because there is a risk of geographical miss of tumors or overdose to OARs. IGRT is an advanced imaging technology that improves the safe clinical application of modern RT techniques (25). IGRT generally means the use of frequent imaging of the patient within the RT treatment room, with the aim of improving the precision of radiation delivery throughout a process of image acquisition, matching with the reference images and setup corrections. Daily IGRT-based setup has been shown to significantly reduce residual errors, and, consequently, planning margins. Currently, several online 2D and 3D imaging devices directly integrated into the LINAC are used, including kilovoltage and megavoltage x-ray imaging, kilovoltage cone beam computed tomography (kV-CBCT), and megavoltage single-slice computed tomography on helical tomotherapy. The simplest online patient positioning verification method is represented by the electronic portal imaging devices, whereby 2D images are captured on a flat panel behind the patient and matched with the digitally reconstructed radiographs of the treatment planning computed tomographic scan. kV-CBCT utilizes a gantry mounted source with a flat panel detector to take a series of X-rays images and to reconstruct a final 3D image. In megavoltage-computed tomography on helical tomotherapy, IGRT is performed by the treatment beam, which rotates around the patient while the couch moves. Since the images are acquired and fused with the reference images, translational and rotational displacements from the expected target position are calculated by software, and then errors are corrected by moving a 6D robotic couch. The quality of images is superior with kV-CBCT compared to the megavoltage imaging (26). The recent ExacTrac/Novalis 6D advanced system allows for accurate positioning comparable to invasive mask fixation (27). A modest set-up difference for intracranial tumors was reported (<1 mm for translations, <1˚ for rotations) when the ExacTrac X-ray 6D (NovalisTx) was compared to the routinely used CBCT (28).

## Proton RT

Protons are positively charged elementary particles, with different physical and biological properties compared to conventional photon radiation. The principal characteristic of these charged particles is the delivery of little energy until the end of their range, known as the Bragg peak, with the highest energy deposition in the target volume and no exit dose. Thanks to these fundamental physical properties, proton RT provides excellent dose distributions to the tumor, while significantly lowering the dose to the surrounding normal tissues.

Proton therapy is increasingly used in pediatric patients with central nervous system tumors with the aim of reducing the potential long-term side-effects of radiation on the development of normal brain tissue in children. For adult and pediatric patients receiving craniospinal irradiation for medulloblastoma, protons may significantly reduce the dose to the cochlea, heart, lung, and kidney, as compared with photons (29-31). For chordomas and chondrosarcomas of the skull base, the use of protons has led to superior results in comparison to conventional photon irradiation, resulting in better clinical outcomes with relatively few significant complications, considering the high doses delivered (32, 33). An excellent tumor control of about 90% at 5 years with low long-term radiation-induced toxicity has been reported with the use of protons in patients with craniopharyngiomas, pituitary adenomas, and meningiomas; however, the reported control and toxicity rates are comparable to those observed with the use of stereotactic photon irradiation (34-36). Randomized clinical trials are warranted to demonstrate the superiority of proton therapy to photon irradiation for brain tumors. In addition, there is a need for long-term follow-up data regarding the different potential risk of developing second tumors following photon and proton therapy.

## Conclusion

RT represents an essential part of the treatment of brain tumors and the past decades have seen significant technological advances in all aspects of radiation delivery. With improved clinical outcomes of cancer treatment, and an increasing number of long-term survivors, minimizing potential RT-related toxicities has also become a priority. New radiation techniques, including IMRT, VMAT, stereotactic techniques, and IGRT allow for more precise treatment delivery, dose-escalation regimens and altered fractionations that can improve tumor control while reducing the volume of healthy tissue irradiated to high doses, and, hence, minimizing the long-term toxicity of radiation treatment. Further studies are needed to compare different RT techniques, in terms of efficacy and long-term toxicity, and investigate the optimal radiation dose/fractionation for each type of brain tumor.

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