



# Radiation Therapy for Non-Malignant Central Nervous System Tumors, Disorders, and Illnesses — Current Applications and Future Directions

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Radiation therapy has a central role in the treatment of various malignant central nervous system tumors, including gliomas, high-grade meningiomas, and brain metastases. This also applies to a plethora of non-malignant central nervous system lesions, such as vestibular schwannomas and arteriovenous malformations, and, in specific situations, for selected functional and psychiatric disorders. In patients with these conditions, the goal of radiation therapy is generally to preserve and stabilize function. In addition, as these illnesses, with some exceptions such as arteriovenous malformations, are rarely life-threatening, the risks of radiation therapy must be interpreted in a different context than for patients with malignancy. Given the continuous and growing interest in the use of radiation therapy for non-malignant tumors and functional conditions, this review summarizes the current and future directions in central nervous system applications, addressing its use for the management of vestibular schwannomas, arteriovenous malformations, trigeminal neuralgia, tremor, Alzheimer's disease, and other psychiatric conditions, such as obsessive-compulsive disorder, addiction, and eating disorders.

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## Introduction

The use of radiation therapy, including stereotactic radiosurgery (SRS) and conventionally fractionated radiation therapy, for the treatment of malignant central nervous system tumors has a long-standing history. This also applies to

a variety of non-malignant lesions, such as vestibular schwannomas, pituitary adenomas, and arteriovenous malformations (AVMs), as well as functional diseases like trigeminal neuralgia (TN). With the recent advances in imaging, radiation techniques, and understanding in functional neuroanatomy, the use of radiation therapy for other diseases,

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such as Alzheimer's disease (AD), addiction, obsessive-compulsive disorder (OCD), and tremor, is emerging and merits further investigation.

In this article, we focus on several established and investigational indications for radiation therapy in non-malignant, though life-altering conditions, where the treatment decision is primarily driven by the goal of preserving function. The primary treatment goal for vestibular schwannoma is to preserve hearing, balance, and facial nerve function, while also preventing symptoms of brainstem compression. Appropriately treated, this tumor is rarely life-threatening. AVM patients endure the stress of living with a lifelong risk of sudden catastrophic bleeding at any time that may result in permanent disability or death. When used in the treatment of TN, radiosurgery is administered purely to control a pain syndrome. Two novel potential applications of radiation therapy are to delay the progression of AD and to disrupt brain pathways driving psychiatric disorders. Although potentially of great benefit, radiation therapy for these 2 fields has been challenging to study due to barriers related to ethics, informed consent, treatment safety, and our limited understanding of the underlying pathophysiology and radiobiology. However, the work is ongoing, and further insights and advances are eagerly awaited.

## Vestibular Schwannomas

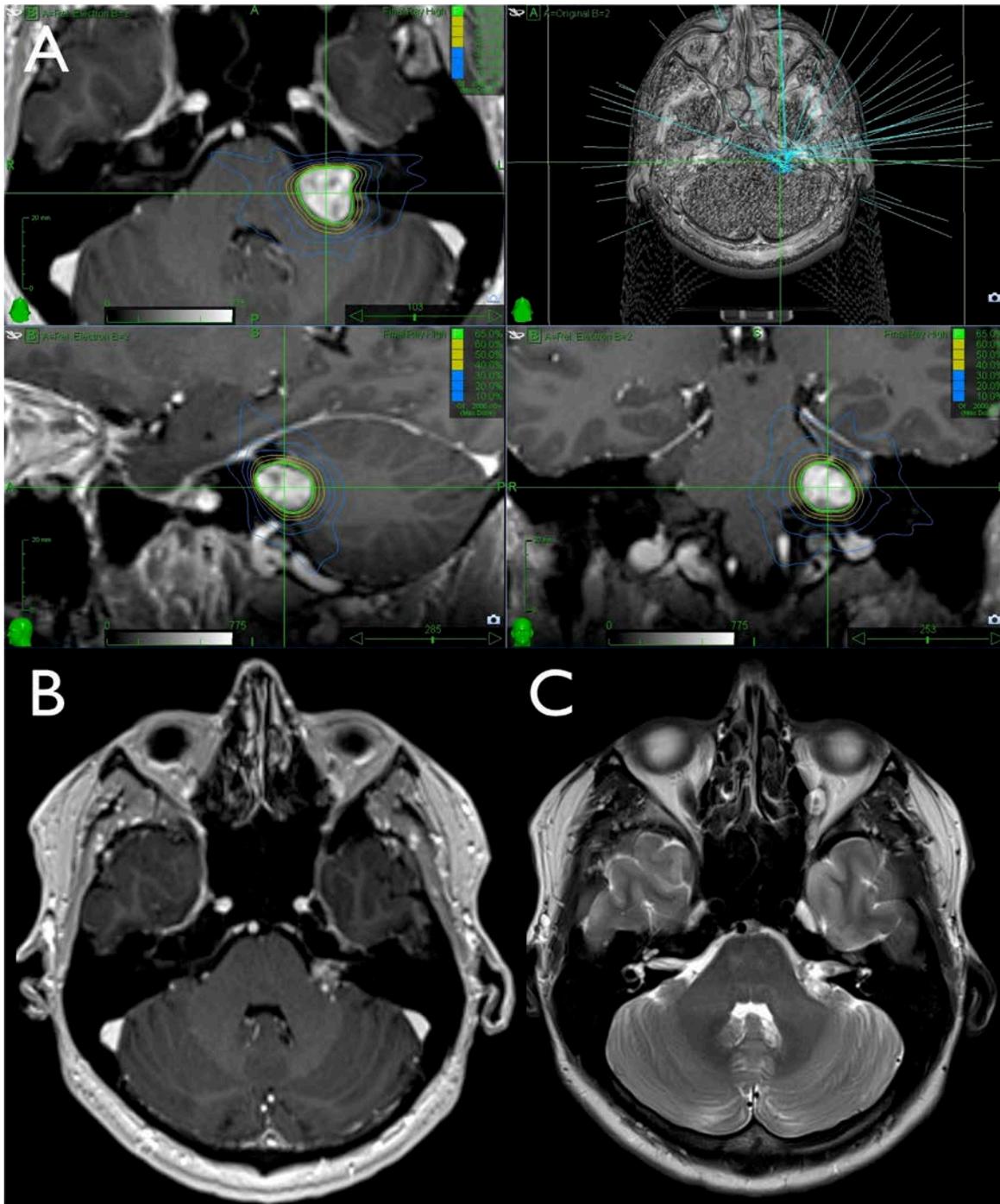
Vestibular schwannomas are benign nerve sheath tumors of the vestibular branch of the vestibulocochlear nerve (cranial nerve VIII), representing the most common tumor in the cerebellopontine angle.<sup>1</sup> Often referred to as "acoustic neuroma," a historical misnomer, they account for approximately 8% of all intracranial tumors and around 75% of all nerve sheath tumors in the central nervous system.<sup>1,2</sup> The incidence of vestibular schwannomas increases with age, with an overall age-adjusted annual incidence of 1.52 per 100,000.<sup>2</sup> In most patients, the tumors are sporadic, while approximately 5% are linked to neurofibromatosis type 2-related schwannomatosis (NF2).<sup>3,4</sup> Bilateral vestibular schwannomas are a diagnostic hallmark distinctive of NF2, occurring in 90%-95% of affected patients.<sup>3</sup> Vestibular schwannomas typically cause gradual hearing loss, tinnitus, vertigo, and dizziness.<sup>5</sup> Significant neuropathy of cranial nerves V and VII is less common but possible.<sup>5</sup> The diagnosis is primarily based on the typical imaging findings on magnetic resonance imaging (MRI) in conjunction with the clinical presentation.<sup>6</sup>

The indication for treatment is based on several factors, including tumor size and growth rate, symptoms, cranial nerve status, patient age and preferences, and comorbidities. In general, the treatment decision-making should be based on an interdisciplinary consensus. While surgical resection may be indicated for tumors causing brainstem mass effect, radiation therapy, particularly with SRS, plays a central role in managing vestibular schwannomas, given its excellent local tumor control and favorable safety profile.<sup>6-9</sup> Therefore, the paragraph will focus on SRS, which may be used for

small- and medium-sized (a)symptomatic tumors, as well as selected larger tumors without a mass effect, to prevent further tumor growth and associated symptoms.<sup>6,7,9,10</sup> SRS also plays a role after a planned subtotal microsurgical resection for cranial nerve sparing in large tumors.<sup>11</sup>

Prescription doses between 11 and 13 Gy for single-fraction SRS are well established, with numerous studies demonstrating excellent outcomes.<sup>6,8</sup> For hypofractionated SRS, 3 × 6 Gy and 5 × 5 Gy are commonly used.<sup>12-14</sup> The question of fractionation is the subject of ongoing debate and research. The recently published ACOUNEU trial compared single-fraction and hypofractionated SRS regarding hearing preservation.<sup>15</sup> No differences were found between both treatment arms, which is in agreement with previous retrospective reports and reviews.<sup>13,16,17</sup> In summary, there is no clear evidence of superiority with fractionation, although some institutions have historically preferred hypofractionated SRS.<sup>15-17</sup> Therefore, single-fraction SRS remains the most common and widely used treatment approach. Nevertheless, the underlying radiobiological rationale may favor fractionated treatments in specific scenarios such as reirradiation. A case-based guide for the management of vestibular schwannomas, including details on the treatment planning and dose constraints for organs at risk, is reported elsewhere.<sup>7</sup> Figure 1 shows a typical SRS treatment plan and treatment response. The treatment-associated toxicity is usually limited, potentially consisting of transient symptom worsening, progressive hearing loss, or edema. High-grade toxicity, such as permanent facial nerve weakness or trigeminal neuropathy, occurs rarely.<sup>18</sup> Malignant transformation or radiation-induced malignancy after SRS is extremely rare.<sup>19,20</sup>

The follow-up after SRS typically includes serial MRI, audiometry, and physical examinations, with the recommendation for structured quality of life assessments.<sup>6</sup> Pseudoprogression, i.e., transient increase in size of the tumor, may be substantial, and must be anticipated during the first 2-3 years of follow-up, whereas actual early progression is unlikely.<sup>21</sup> However, cases of pseudoprogression have also been reported after 3 years, highlighting the need for a careful assessment.<sup>21,22</sup> Approximately one-third of patients can have pseudoprogression after radiosurgery, which should not be categorized as treatment failure.<sup>23-25</sup> Actual local tumor progression must be carefully confirmed, considering the time since SRS, longitudinal volumetric changes, and symptoms.<sup>21,22</sup> A continuous, uninterrupted tumor volume increase over 2-4 years after radiosurgery with worsening symptoms, such as impaired hearing, is indicative of actual tumor progression.<sup>7,21</sup> An initial increase in tumor volume, followed by a decrease, i.e., pseudoprogression, in the first years after SRS, succeeded by further tumor growth and true progression, is observed in a smaller proportion of patients.<sup>21</sup> The outcomes after radiosurgery are favorable. Local tumor control is typically achieved in over 90% of cases without the need for further treatment.<sup>18,26</sup> There is limited prospective data addressing whether there is a benefit of early intervention for selected vestibular schwannoma versus observation. The recently reported V-REX trial



**Figure 1** (A) Treatment plan for a left vestibular schwannoma. Single-fraction stereotactic radiosurgery, prescription dose 13 Gy, prescription isodose line 65%, planning target volume 1.83 cm<sup>3</sup>. (B/C) Magnetic resonance imaging, T1-weighted contrast-enhanced (left) and T2-weighted images (right), 17 months after treatment, demonstrating treatment response and loss of contrast enhancement.

investigated whether radiosurgery for small- and medium-sized vestibular schwannomas is superior compared to a wait-and-scan approach in terms of tumor control.<sup>27</sup> The primary endpoint was the tumor volume ratio at the end of the trial, after the four-year follow-up, and the start of the trial. Secondary endpoints included 26 outcomes, including patient-reported outcomes and quality of life assessments. The trial showed excellent tumor volume control with SRS.

Only 3 patients in the radiosurgery arm required treatment for further tumor growth, while 22 patients in the wait-and-scan arm underwent additional treatment. Notably, 25 out of the 26 secondary outcomes demonstrated no significant differences. These findings align well with the VISAS-K1 and VISAS-K2 studies, two retrospective, propensity score-matched multicenter analyses, comparing SRS for Koos grade 1 and 2 tumors with active surveillance.<sup>28-30</sup> Based on

the available evidence, the findings suggest that either an early intervention with SRS or observation for selected small vestibular schwannomas is appropriate.<sup>31</sup> Nevertheless, further prospective research is vital to refine the management of vestibular schwannomas, including the optimal timing for treatment.

Patients with confirmed tumor progression have several treatment options, depending on the tumor size, comorbidities, personal preferences, and previous treatments. It must be acknowledged that treatment algorithms for local tumor progression are less well-defined. This underlines the necessity for a careful, interdisciplinary approach. Microsurgical resection after prior irradiation has been associated with a high risk of facial nerve injury, and this risk is considered in the decision of some patients as a "risk" of the selection of radiosurgery in the initial management. Based on the limited evidence available, reirradiation with SRS of truly progressive tumors after initial radiosurgery represents a viable salvage treatment, with an acceptable safety profile.<sup>32</sup>

In summary, radiation therapy, especially SRS, is a central treatment modality for vestibular schwannomas. Based on the plethora of studies and reports, SRS provides an excellent long-term tumor control with a low risk of significant and persistent treatment-associated toxicity. The role of reirradiation, potential differences between single-fraction and hypofractionated SRS, timing of treatment, and further approaches to preserve hearing and cranial nerve function in patients are some of the topics that will most likely be addressed by future research in the field.

## Arteriovenous Malformations

In 1967, Lars Leksell had advanced the concept of SRS that he initially proposed in 1951 with the deployment of the first Gamma Knife.<sup>33</sup> Based on the observation that conventional radiation used for tumors could induce vascular narrowing, Steiner in 1970 used the first Gamma Knife in an attempt to ablate an AVM.<sup>34</sup> Using planar angiography to guide the treatment, SRS was delivered to the feeding vessels of the malformation. Although no changes were observed on the 4-month follow-up angiography, an angiogram obtained 19 months later demonstrated complete resolution of the AVM.

Since that pioneering experience, there has been considerable interest in elucidating the biological processes responsible for the gradual obliteration of AVMs, which typically unfolds over several years.<sup>35-37</sup> The earliest observed changes include endothelial cell injury, which becomes apparent within days of irradiation. This is followed by the circumferential proliferation of smooth muscle cells, and subsequently, the progressive deposition of hyaline material and dense collagen that gradually occludes the small muscularized vessels of the nidus, occurring over a period of years. It remains unclear whether the therapeutic ratio of radiosurgery is determined solely by precise targeting or whether intrinsic structural and functional abnormalities within AVM

vasculature also contribute to radiosensitivity. Additionally, it is intriguing to consider whether similar vascular effects may underlie the effectiveness of high-dose radiosurgery in the treatment of certain tumors.

The motivation for the treatment of patients with AVM is the risk of brain hemorrhage that can be fatal or result in disability. Cerebral AVMs can present with a variety of signs and symptoms, including headaches, seizures, transient focal neurologic deficits, and hemorrhage. Once the abnormality is identified, the future risk of bleeding is estimated to be 2%-4% for each year of life, with each bleeding event associated with a 20%-30% fatality risk and a 20%-40% rate of permanent disability.<sup>38-41</sup> Significant risk factors for future hemorrhage of untreated lesions in individual patients include prior bleeding, deep brain location, and entirely deep vein drainage.<sup>42</sup> Patients with none of these risk factors appeared to have a less than 1% risk of bleeding per year of follow-up without treatment, whereas those with all factors had a risk of 34% per year. Interestingly, the size of the AVM itself may not always be an essential factor.

There is no disagreement that surgical resection, or, in a small number of patients, endovascular obliteration are the treatments of choice to prevent AVM hemorrhage. However, for patients with AVMs that cannot be resected or obliterated safely due to their volume, location, and venous drainage, radiosurgery is an effective non-invasive treatment option for ablating AVMs. Nevertheless, a substantial disadvantage is that the risk of hemorrhage persists for several years, occasionally stretching over a decade, until complete resolution, i.e., obliteration, of the AVM. Radiosurgery is most successful for lesions smaller than 3-4 cm in size, with geometry and location in the brain that allow for a dose of 18 Gy or higher to be administered without unacceptable risk of injury. The response is dose-related.<sup>43</sup> When 18 Gy or higher can be given to a volume including the periphery of the AVM, the ablation rate is 80% or higher.<sup>43-45</sup> The obliteration rate appears to plateau at approximately 90% at a dose of roughly 20-22 Gy, with marginal benefits with increases beyond that. The imprecision of angiography in identifying the entire extent of the AVM nidus in some patients may be the cause of the cap on success with increasing dose. For doses between 14 and 16 Gy, the resolution rate ranges from 50% to 60%.

The decision on the dose to be administered, with the goal of at least 18-20 Gy, depends upon the maximum that can be given with appropriate safety, and which becomes a challenging goal as lesion size reaches 3-4 cm. However, considerable injury from radiosurgery has not been most closely correlated with the size of the lesion treated with a high dose, but with the volume of brain, including normal tissue exposed to 12 Gy or more, and the eloquence of that region.<sup>46,47</sup> Flickinger reported the specific risk of injury related to dose based on eloquence location in the brain, which provides guidance on the appropriate safety of the planned radiation dose.<sup>47</sup> The highest risk regions of the brain included the brainstem, thalamus, and corpus callosum. However, a nuanced consideration of the function of

the localized area of the brain is critical, such as the motor strip and visual cortex. Pretreatment embolization may be used to reduce the size of a lesion to enable higher dose radiosurgery, but has actually been associated with inferior outcome, perhaps because of an impact on radiation dosimetry of the material and/or on visualization of the lesion on the angiogram to define a true target.

Importantly, there are strategies to use radiosurgery effectively as an alternative to surgery, even when a dose likely to be curative cannot be administered in a single fraction. First, there is extensive experience in safely retreating high-dose AVMs that were treated with curative intent, generally after allowing a 3-year or longer interval to confirm that there has been no adequate response to the initial treatment. The obliteration rate is approximately 60% despite failure of the initial treatment, and the radiation injury rate is around 10%.<sup>48-51</sup> Staged treatments, however, include treating part of an AVM to an effective dose with a plan to treat the remainder at a planned interval of generally 6-12 months.<sup>38,48,52-54</sup> With this strategy, an obliteration rate of 60%-70% is anticipated if a dose of 17 Gy or greater is ultimately administered to the entire nidus. Other approaches use low-dose treatment of 10-14 Gy to the entirety of a large lesion with an understanding that retreatment, as described above, will be required.<sup>55,56</sup> The ARUBA trial has raised the question of whether lower-risk AVMs that have not ruptured should be treated.<sup>57,58</sup> Participants were randomized to either medical management alone or medical management with an intervention selected by the treating physicians. The study was closed after enrollment of 226 of 800 planned patients, as treated patients had an inferior early outcome of stroke or death. With a mean follow-up of 50.4 months, the hazard ratio of 0.31 was superior for medical management alone.<sup>58</sup> Still, concerns have been raised about the general applicability based on issues related to design and conduct of the study including selection bias, participating-site characteristics, high inclusion of embolization in therapy, lack of standardized approaches to therapy selection, no stratification for important risk factors, worse than expected outcomes for interventions, and short length of follow-up for a lifelong condition in which further toxicity is not likely once obliterated with treatment.<sup>38,39,59-61</sup> In contrast, the morbidity and mortality of untreated lesions are likely to continue increasing over time. Therefore, decisions for this group should continue to be personalized based on the risk of future bleeding and the suitability of different therapeutic options.

Although SRS has a well-documented effectiveness in treating AVMs, multidisciplinary involvement in decision-making is critical. Important factors include the lifetime risk of monitoring, whether immediate surgical cure is feasible and safe, patient goals, and whether a sufficient dose of radiation can be given, sometimes over several treatments, to result in an ablation of the lesion. The delayed resolution of the lesion with irradiation and continued risk of bleeding during that interval is an important consideration, especially for patients at high risk of future hemorrhage. The Spetzler-Martin grading system, based on adverse features such as large size, location in eloquent brain areas, and deep venous

drainage, has been used to categorize patients based on predicted surgical outcome, and is used not only to guide selection among management options but also to divide patients into more homogeneous groups, facilitating comparison of outcomes of different strategies.<sup>62</sup> Several comparative studies and meta-analyses of relevant literature suggest that the cure rate is higher with surgical intervention, but that the risks of radiosurgery are lower.<sup>59,63-67</sup> However, there are many undefined factors beyond the Spetzler-Martin grade that are unique to the anatomy of each patient's AVM and their clinical circumstances, which determine whether the patient will be triaged to surgical resection or radiosurgery. The Virginia grading system has been developed to similarly categorize patients treated with radiosurgery based on adverse factors such as age above 65 years, large AVM size, eloquent brain location, and prior embolization.<sup>68</sup>

## Trigeminal Neuralgia

TN is a prototypical paroxysmal facial pain disorder, affecting approximately 4-13 per 100,000 persons per year.<sup>69,70</sup> Drug therapy, such as carbamazepine or oxcarbazepine, remains first-line, but 30%-50% of patients eventually require additional intervention.<sup>71-73</sup> Contemporary options include microvascular decompression (MVD), radiofrequency rhizotomy, balloon compression, glycerol rhizolysis, and SRS. Compared with open or percutaneous techniques, SRS is a non-invasive procedure and is performed as an outpatient treatment with minimal adverse effects, making it an attractive choice for elderly or medically frail patients.<sup>74-76</sup>

## Historical Perspective

Dandy's 1930s observation that arterial loops compressing the trigeminal root-entry zone could be surgically mobilized marked the beginning of the modern era of MVD.<sup>77</sup> Jannetta later refined the procedure, reporting durable pain relief in more than 80% of carefully selected patients.<sup>78</sup> Meanwhile, Spiegel and Wycis's stereotactic frame (1947) and Leksell's Gamma Knife (1968) paved the way for an incision-less treatment.<sup>74,79</sup> In 1992, the Karolinska group published one of the first clinical reports of Gamma Knife rhizotomy, showing that a single 70-90 Gy shot to the trigeminal root-entry zone could reduce pain without craniotomy.<sup>80</sup> Régis and colleagues confirmed long-term efficacy in a 497-patient European cohort.<sup>81</sup> Image-guided, mask-based linear accelerator and CyberKnife solutions appeared in the 2000s, broadening access and facilitating prospective studies.<sup>76,82</sup>

## Pathophysiology and Target Selection

Episodes of TN are believed to arise from cross-talk between demyelinated fibers at the dorsal root entry zone. High-resolution diffusion-weighted imaging shows that the radiosurgically responsive target is the ~3 mm root-entry zone, where central (oligodendrocytes) myelin transitions to peripheral (Schwann cells) myelin.<sup>83</sup> Tractography-based planning

helps center the 4-mm isocenter on this vulnerable zone while sparing adjacent fibers.<sup>84</sup>

## Current Interventional Paradigm

MVD remains the gold standard for young, medically fit patients with demonstrable vascular conflict, offering the highest long-term cure rate (>80% at 10 years).<sup>85</sup> Percutaneous intervention yields rapid relief but carries a 10%-30% risk of dysesthesia or anesthesia dolorosa, especially after repeat procedures.<sup>74</sup> In contrast, SRS has a different post-treatment course: pain relief typically begins after 4-8 weeks, while severe sensory morbidity is <5%.<sup>81,86</sup> Notably, focused ultrasound is still investigational for TN, and unlike SRS, it is limited by skull-density constraints.

## Radiosurgical Technique

Thin-slice constructive interference in steady state (CISS) or fast imaging employing steady-state acquisition (FIESTA) MRI and computed tomography (CT) are used to delineate the cisternal trigeminal nerve. On Gamma Knife, a single 4-mm collimator typically receives 80-90 Gy at the 100% isodose, with the 20%-30% isodose kept outside the pontine border (<15 Gy). Linear accelerator and CyberKnife systems use cones or multi-leaf collimators to produce similar dose distributions with submillimeter image guidance.<sup>76,82,87</sup>

## Efficacy and Toxicity

TN-associated pain is often graded with the Barrow Neurological Institute (BNI) scale, with documentation of the medication use.<sup>88</sup> A pooled analysis of more than 1100 published cases shows that 60%-75% achieve complete pain freedom without medication (BNI I) by 12 months, while an additional 10%-15% enjoy worthwhile improvement on reduced drug doses.<sup>86</sup> The median latency to initial response is 6 weeks. The five-year pain-free durability rate is approximately 50%. Late recurrence can often be salvaged with a second radiosurgical rhizotomy, which restores durable control in two-thirds of cases.<sup>89</sup> In cases of patients with bilateral TN, staged SRS performed  $\geq 12$  months after the initial treatment achieved  $\leq$ BNI IIIb pain relief in 87% of first-treated nerves and in 95% of second-treated nerves. Estimated durability after the repeat procedure was 89% at 1 year and 62% at 5 years, with bothersome numbness in  $\leq 20\%$  and no cases of anesthesia dolorosa.<sup>90</sup> Patients are typically examined at 6 weeks, 3 months, and 1 year, with further follow-up visits depending on the control of clinical symptoms and the effectiveness of medical management. SRS is the least morbid of all procedural options for TN. Mild, non-bothersome facial numbness occurs in 7%-20% of patients. The rate of troublesome dysesthesia is <5%, and objective corneal reflex loss is <1% when the pontine dose is limited. Anesthesia dolorosa and brainstem injury are exceedingly rare with modern planning constraints. Importantly, quality of life studies show that even patients who develop mild numbness rate their outcome as favorable because pain relief outweighs sensory changes.<sup>81,86</sup> Extrapolation from the literature on essential

tremor (ET), end-to-end cost analyses indicate that single-fraction SRS is more cost-effective than MVD for unilateral disease, as it involves no hospital stay.<sup>91</sup>

## Future Directions and Conclusion

Ongoing studies are investigating the role of hypofractionated radiosurgery, such as 72 Gy in 6 fractions, in reducing facial numbness associated with single-fraction radiosurgery.<sup>92</sup> Integration of magnetic resonance-linear accelerator technology promises real-time imaging and adaptive dosimetry, while connectome-based targeting aims to personalize the isocenter to each patient's fiber anatomy. Ultimately, predictive radiobiological modeling may enable proactive reirradiation schedules that extend pain freedom beyond the current 5- to 7-year plateau. In summary, SRS provides durable pain control for most medication-refractory TN patients, with a favorable safety profile among ablative procedures. Its non-invasive nature, outpatient workflow, and compatibility with anticoagulation make it the interventional choice for the elderly, the medically fragile, and those who decline open surgery, while leaving MVD available as a future therapeutic option.

## Tremor

Tremor is a highly prevalent movement disorder, affecting about 7 million people in the United States and roughly 6% of adults older than 65 years.<sup>93,94</sup> ET constitutes the majority of cases, followed by tremor-dominant Parkinson's disease and the less frequent symptomatic tremors of multiple sclerosis, stroke, or trauma. First-line medications include propranolol or primidone.<sup>95</sup> However, approximately 30%-50% of patients fail to respond to these drugs.<sup>95</sup> For this population, interventional therapy becomes necessary. Contemporary options include deep brain stimulation (DBS) of the ventral-intermediate nucleus (VIM), radiofrequency thalamotomy, magnetic resonance-guided focused ultrasound thalamotomy, and SRS.<sup>96-100</sup> Among them, SRS is the only non-invasive technique that requires neither general anesthesia nor interruption of anticoagulation, making it particularly attractive for older and frail patients, as well as non-surgical candidates.<sup>100</sup> Patients being considered for such treatment should be under the care of a neurologist and neurosurgeon with demonstrated expertise in the management of movement disorders.

## Historical Perspective

The search for a safe and effective treatment method spans nearly a century. Early open cortical or pyramidal tract surgeries performed in the 1930s reduced tremor but left unacceptable motor deficits.<sup>97</sup> Progress accelerated when Spiegel and Wycis introduced the first human stereotactic frame in 1947, creating a reproducible three-dimensional coordinate system for deep targets.<sup>79</sup> Seven years later, Hassler and Riechert electrophysiologically mapped the thalamus and identified the VIM as the critical relay for tremor.<sup>101</sup> Subsequent

decades produced a parade of innovations: Velasco's description of the posterior subthalamic area in 1972, Benabid's demonstration of high-frequency VIM stimulation in 1987, the birth of DBS, and Duma's landmark 1998 report of Gamma Knife thalamotomy for tremor.<sup>100,102</sup> Linear-accelerator thalamotomy became feasible in 2004, while pilot and randomized trials by Elias and colleagues between 2013 and 2016 validated thermal lesioning with magnetic resonance-guided focused ultrasound thalamotomy.<sup>98,99,103</sup> A cost-utility analysis later showed that both SRS and focused ultrasound thalamotomy were more economical than DBS for unilateral ET, supporting its use in the treatment of this disease, even as a first-line therapy in selected patients.<sup>91</sup>

### Pathophysiology and Target Selection

Functional imaging, diffusion-tensor tractography, and electrophysiology converge on a cerebello-thalamo-cortical network: Oscillations initiated in the dentate nucleus travel along the dentato-rubro-thalamic tract (DRT), synapse within the VIM, and reverberate to the primary motor cortex.<sup>104</sup> Lesioning or stimulating the VIM interrupts this loop and reliably suppresses tremor. In modern practice, patient-specific tractography can delineate the DRT and adjacent internal capsule, allowing millimetric refinement of the radiosurgical isocenter.<sup>105</sup>

### Current Interventional Paradigm

The choice of treatment modality for medication-refractory ET is tailored to the individual patient. DBS offers reversible, adjustable control and remains the gold standard for long-term control of bilateral disease in medically fit patients, yet it requires craniotomy and implanted hardware with infection and maintenance risks.<sup>96</sup> Radiofrequency thalamotomy provides immediate relief but is invasive and carries a  $\leq 10\%$  rate of permanent neurological deficits, especially if performed bilaterally.<sup>97</sup> Magnetic resonance-guided focused ultrasound thalamotomy delivers real-time MRI guidance and rapid benefit, but excludes patients with unfavorable skull density and still lacks long-term data.<sup>106</sup> SRS is unique in being completely outpatient, frame-based, or mask-based, and compatible with anticoagulation, while its main drawbacks are the 6-12 week latency to effect, the absence of intraoperative confirmation, and the required latency period of 12-24 months, following treatment of one side, to treat the other.<sup>100</sup>

### Radiosurgical Technique

SRS is offered for medication-refractory ET, tremor-dominant Parkinson's disease, and carefully selected symptomatic tremors. It plays an especially valuable role when open surgery is undesirable or not feasible. Mask- or frame-based radiosurgical techniques are available. On stereotactic MRI, the VIM is located approximately 11 mm lateral to the third ventricle wall, 2-3 mm superior to the plane of the anterior and posterior commissures, and is positioned 1/4th of the

way anteriorly from the posterior commissure toward the anterior commissure. A single 4-mm isocenter is treated with 130-140 Gy on the Gamma Knife or a biologically matched 110-140 Gy on linear accelerators, while sparing the internal capsule and sensory thalamus.<sup>107-110</sup>

### Efficacy and Safety

Neurological examination and Fahn-Tolosa-Marin (FTM) scoring are typically performed at 3, 6, and 12 months, with MRI at 6-12 months used to document the signature lesion. Across prospective studies and large series, unilateral SRS achieves significant tremor reduction in 70%-90% of patients, with responder definitions ranging from  $\geq 50\%$  FTM improvement to complete arrest.<sup>106-119</sup> Benefit typically begins 8-12 weeks after treatment and plateaus by 6-12 months. Long-term follow-up shows durable control beyond 5 years in most responders.<sup>114</sup> Adverse events are predominantly mild and transient. Sensory disturbance and gait ataxia each occur in  $<10\%$  of cases; permanent disabling deficits are uncommon,  $\leq 4\%$ - $8\%$  across contemporary series.<sup>119</sup> A network meta-analysis of 464 focused ultrasound and 62 SRS thalamotomies for ET found equivalent 12-month tremor suppression but a four-fold higher rate of persistent adverse effects after focused ultrasound – imbalance (10.5%) and sensory disturbance (8.3%) – compared with SRS – transient hemiparesis (2.7%) and dysarthria (2.4%). The authors linked focused ultrasound toxicity to larger, ellipsoid thermal lesions and skull-density constraints, whereas SRS lesions are smaller, spherical, and evolve slowly, sparing adjacent capsule fibers. These data reinforce SRS as a safer, non-invasive treatment option when long-term tolerability is paramount.<sup>120</sup> Cost-utility analyses favor SRS and focused ultrasound thalamotomy over DBS for unilateral ET, primarily because hardware and postoperative programming costs are absent.<sup>91</sup>

### Future Directions and Conclusion

Connectome-guided targeting personalizes the isocenter to each patient's DRT, and optimized dose de-escalation studies designed to minimize hyper- and hyporesponders are anticipated developments in the field. Finally, staged bilateral SRS, which is already showing approximately 80% contralateral control without excess toxicity in small series, may expand options for patients unsuited to DBS.<sup>121</sup> In summary, SRS thalamotomy delivers durable tremor suppression in most medication-refractory patients while avoiding operative morbidity and implanted hardware. Contemporary evidence supports a lower toxicity for SRS compared with focused ultrasound. Ongoing advances in imaging, radiobiology, and delivery will help refine radiosurgery as an important tool for individualized tremor care.

### Alzheimer's Disease

AD was initially described in 1906 by the German psychiatrist Alois Alzheimer, who then published the results of an

autopsy study that identified neurofibrillary tangles and plaques.<sup>122</sup> That report initiated an ever-expanding effort to identify the exact reason for the development of these findings. However, the efforts made since then in search of an effective treatment have yielded mixed results. In 2024, it is estimated that nearly 7 million Americans age 65 or older are suffering from AD, with the median lifespan from AD diagnosis to death of 7-10 years.<sup>123,124</sup> It also notably increased healthcare expenditures, not only in direct costs of approximately \$384 billion, but also in indirect costs of \$413.5 billion, including unpaid caregiving, as well as significant productivity losses.<sup>123</sup> In the future, it is estimated that the number of patients in the United States with AD will more than double and will be responsible for ever-increasing competition for healthcare dollars from governmental, self-pay, and non-reimbursed perspectives.<sup>125</sup> Disappointingly, up to this point, there has been limited progress in stopping or slowing the symptoms of AD.

## Pharmaceutical Developments

The pharmaceutical industry has taken an active interest in developing pharmaceuticals addressing AD, with billions of dollars spent to date. Several phase 3 trials are ongoing or have been recently completed, assessing the effectiveness of amyloid-targeting therapies. The monoclonal antibodies aducanumab, donanemab, and lecanemab each target different epitopes or have different binding affinities to the various forms of amyloid beta ( $A\beta$ ). Aducanumab targets aggregated forms of  $A\beta$ , and the EMERGE phase 3 trial demonstrated a statistically significant reduction in clinical decline, whilst a second trial, the ENGAGE phase 3 study, did not replicate this finding.<sup>126</sup> Although the drug was controversially approved by the Food and Drug Administration (FDA) in 2021, it was later discontinued by the manufacturer. Lecanemab targets soluble  $A\beta$  protofibrils, which are intermediate structures formed during the aggregation of  $A\beta$  peptides that are believed to be toxic. Lecanemab was granted approval by the FDA in 2023 after showing a 27% lower Clinical Dementia Rating-Sum of Boxes in the experimental arm after 18 months in a phase 3 trial.<sup>127</sup> Donanemab targets a modified form of deposited  $A\beta$  and received FDA approval in 2024 after results from the TRAILBLAZER-ALZ 2 trial.<sup>128</sup> The primary endpoint of the study, the integrated Alzheimer's Disease Rating Scale, exhibited a 35.1% delay in clinical decline at 76 weeks in the donanemab group compared with the placebo group. Yet, even though the FDA has approved certain drugs, none have demonstrated a significant long-term impact in delaying the progression of AD or overall survival, and only a few have shown a slight slowing of symptoms based on neurocognitive scores when compared to matched cohorts.<sup>129-131</sup>

The pharmaceutical companies and research institutions have taken multiple approaches. They have included targeting various points along the development lines for both amyloid and tau. However, while animal models have demonstrated effectiveness for some of these drugs, this has not translated well to humans, highlighting the multifactorial

nature of causation. Despite the disappointing effectiveness of current agents, approved drug therapy is expensive, whereas a short course of radiation therapy, if durably effective and safe, would be cost-effective and readily available in most healthcare systems worldwide.

## Origins of the Low-Dose Radiation Concept to Treat Alzheimer's Disease

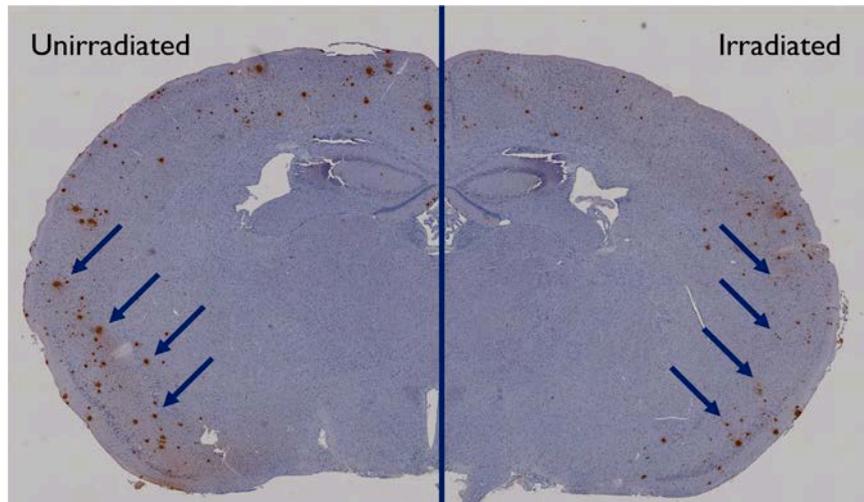
About 15 years ago, the initial concepts for low-dose radiation as a potential treatment for AD developed from family experience of the disease and curiosity about a peripherally related population of children, namely those with Down syndrome who had received whole-brain irradiation for acute lymphocytic leukemia. It is expected that up to 90% of these children would have developed AD.<sup>132</sup> However, discussion with their treating physicians and review of the literature failed to find any mention of plaques in these children at the time of death. This led to the hypothesis that low-dose radiation therapy might have a beneficial effect on the development of AD plaques.

## Initial Studies and Proof of Concept

To test this theory, a series of animal studies was performed using a well-characterized double transgenic mouse model expressing a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9) (APP/PS1) to determine whether radiation could favorably impact the development and/or clearance of amyloid plaques. Utilizing a hemi-brain irradiation technique, which allows for the direct comparison of irradiated and unirradiated brain in the same histological section, initial experiments investigated single doses of 5, 10, and 15 Gy and found a dose-response relationship in the reduction of  $A\beta$  plaques (Fig. 2). However, subsequent experiments with fractionated doses showed a greater reduction in plaques as a function of biologically effective dose, providing the first indication that the effect was not classical cell killing, as seen in oncology.<sup>133</sup> From these second-generation hemi-brain experiments, 5 fractions of 2 Gy emerged as a preferred radiation therapy schedule. This was used in subsequent experiments involving whole-brain irradiation in older animals exhibiting significant cognitive deficiencies. Using a standard Morris water maze test, the irradiation resulted in cognitive improvements measured by latency accessing a concealed platform.<sup>133</sup> Furthermore, the improvement in cognition correlated with a reduction in plaque burden confirmed on post-water maze testing histological samples.<sup>133</sup> Later, the same effect on  $A\beta$  plaque reduction was demonstrated in the B6;129-Tg(APP<sup>Swe</sup>,tau<sup>P301L</sup>)1Lfa Psen1<sup>tm1Mpm</sup>/Mmjax (3xTg-AD) model, which harbors both amyloid and tau mutations; changes in tau expression were also observed.<sup>134</sup>

## Development of a Phase I Trial

After several years of animal model studies, the logical conclusion was to move forward with a single-arm phase 1 clinical trial in patients with moderate AD. After careful



**Figure 2** Section of APP/PS1 mouse brain treated with hemi-brain irradiation of  $5 \times 2$  Gy, sacrificed 8 weeks later. Blue arrows highlight the reduction of A $\beta$  plaques in the irradiated hemi-brain.

consideration of the preclinical data and low-dose regimens used in pediatric hematologic cancers for whole-brain prophylactic cranial irradiation with low risk of later malignancy, a dose of  $5 \times 2$  Gy was selected.<sup>135</sup> This AD trial design was shared with several other groups and investigated the optimal irradiation scheme observed in the preclinical studies, which involved  $5 \times 2$  Gy as consecutive fractions administered over a single week.

Unfortunately, the study was terminated due to poor accrual resulting from the challenges of patient recruitment during the COVID-19 outbreak. However, two centers, one in Virginia and one in Geneva, were able to accrue enough patients to allow for neurocognitive testing to be completed for up to 18 months after treatment completion. It appeared that the selected radiation dose had a positive impact on stabilizing or even improving symptoms in patients with early AD.<sup>136</sup>

### Expansion of Low-Dose Radiation Therapy Studies

In the intervening years between the original observations and the present day, numerous experimental studies have pursued this line of investigation, demonstrating a spectrum of potentially beneficial effects of low-dose radiation treatment for AD.<sup>134,136-144</sup> Some major questions persist, including what is the optimum dosing schedule, how long does the radiation effect persist, and whether retreatment is possible and efficacious? Several mechanisms have been suggested for the effect of low-dose radiation in this disease and have been reviewed in various publications.<sup>145-148</sup> A definitive mechanism has yet to be identified. It would seem that the effect is pleiotropic and may open up opportunities for novel combinations with current and new other available or yet-to-be-developed treatment modalities.

### The Implications for Radiation Therapy

The potential of this treatment strategy has obvious ramifications for the radiation oncology community and the

manufacturers of linear accelerators. This has led to the formation of a collaborative trial group, comprising multiple centers in Europe and the United States, to develop an international phase 2 clinical trial addressing this opportunity in greater detail. There are frequent and ongoing discussions among members of a multidisciplinary, international steering group. A three-arm trial, which includes observation with standard of care and two separate low-dose irradiation cohorts, enjoys great enthusiasm. The two proposed low-dose dose arms are  $5 \times 2$  Gy delivered consecutively over 5 days or  $5 \times 0.5$  Gy over the same timescale. Additionally, a comparable Korean trial is currently underway.<sup>149</sup> Efforts such as this will help define whether low-dose radiation is effective in slowing the progression of AD, but in the words of Albert Szent-Györgyi, “research is to see what everybody else has seen and to think what nobody else has thought.” In many ways, the concept of treating a neurodegenerative disease with radiation falls into this realm, and the potential success would be significant for countless patients and families, and in essence, every healthcare system worldwide.

### Psychiatric Disorders

Approaches to understanding and treating psychiatric disorders have evolved throughout history in response to shifting hypotheses of pathophysiology, treatment paradigms, and societal attitudes. Texts from ancient civilizations reveal an appreciation for the biological bases of psychiatric disorders, as Hippocrates proposed that melancholy (from Greek *μέλαινα χολή* (melaina chole), translated as “black bile”) was the result of an imbalance of the 4 bodily humors in 450 BCE.<sup>150,151</sup>

In the late 19th century, various “somatic” approaches to treating psychiatric disorders were developed. By the 1930s, the increasing trend towards hospitalization of patients with these disorders and subsequent severe overcrowding in public institutions opened the door to surgical treatment.<sup>152,153</sup> Egas Moniz, a Portuguese neurologist, partnered with

neurosurgeon Almeida Lima to perform “frontal leucotomies.”<sup>154</sup> The reported results were sufficient to spark international interest in this approach, and Moniz was awarded the Nobel Prize in Physiology or Medicine in 1949.<sup>155</sup> Walter Freeman, an American neurologist, worked with neurosurgeon James Watt and altered Moniz’ technique to perform “frontal lobotomies.”<sup>156</sup>

Neurosurgeons around the world, with enthusiastic support from psychiatrists, continued to modify ablative surgical approaches for patients with mental disorders. The most common diagnoses treated were OCD and schizophrenia.<sup>157</sup> Ultimately, the emergence of neuroleptic medications in the mid-1950s, paired with growing social pressure over abuses in psychiatric surgery, led to its decline.<sup>155</sup> However, a small number of practitioners around the world continued to work on minimally invasive stereotactic procedures for these patients.<sup>158</sup> In fact, the US government-commissioned Belmont Report recommended, in 1979, that psychiatric surgery continue to be offered to select psychiatric patients.<sup>156</sup>

Recent advances in neuroimaging, stereotactic techniques, and ethical frameworks, combined with the persistence of treatment-resistant psychiatric disorders, have renewed interest in alternative therapeutic modalities for neuromodulation.<sup>159-161</sup> Today, FDA-approved indications for invasive intracranial neuromodulation are quite limited.<sup>162</sup> Interventions for other indications remain at an investigational stage, and the role of invasive procedures such as DBS or radiofrequency ablation versus non-invasive methods such as SRS or focused ultrasound remains a subject of debate.<sup>163</sup> Given the historical context and implications of irreversible brain interventions, SRS has correspondingly been studied with great caution. Here, we review the evidence for radiation therapy, SRS in particular, in defined, intractable psychiatric disorders.

### Obsessive-Compulsive Disorder

With a lifetime prevalence of 1%-3%, OCD is characterized by obsessions, i.e., intrusive and disturbing thoughts, and/or compulsions, i.e., repetitive and obsessive behaviors.<sup>164-168</sup> In OCD, the cortico-striato-thalamo-cortical loop is dysregulated from hyperactive excitatory pathways and a hypoactive inhibitory pathway.<sup>169</sup> Approximately 30% of patients display an inadequate response to first-line therapies, including cognitive behavioral therapy and serotonin reuptake inhibitors, leading to their evaluation for alternative therapeutic modalities.<sup>170,171</sup> SRS is gaining interest as a treatment option for patients with severe treatment-refractory OCD. The anterior limb of the internal capsule, a hyperactive communicating white matter tract connecting the prefrontal areas and subcortical gray matter, has been investigated as a radiosurgical target since 1951.<sup>172</sup> A recent meta-analysis of 11 studies with 180 patients targeting this area with SRS determined that 60% of patients experienced a substantial improvement in OCD symptoms.<sup>173</sup> Encouragingly, remission was achieved in 18% of patients, and long-term follow-up data showed sustained post-SRS response at a mean of 10.9 years. In a separate 14-patient study, the most common

adverse effects were headaches (15%), weight changes (14%), and mood changes (9%), with no significant changes in personality measures.<sup>174</sup>

While the ventral portion of the anterior limb of the internal capsule has emerged as the most studied target to date, additional considerations, such as optimization of dose, refinement of target, and customization for individual neuroanatomical heterogeneity, remain a subject of ongoing discussions to maximize treatment response and minimize adverse effects.<sup>172,175,176</sup> Anterior capsulotomies have been applied with doses ranging from 120 to 200 Gy in 1-4 fractions.<sup>177</sup> Dorsal anterior cingulotomies have also been investigated as alternatives.<sup>175</sup> Though SRS may not reduce the need for medications and psychiatric care, it presents a potential augmentation therapy for patients with severe OCD.<sup>178,179</sup>

### Bipolar Disorder

Bipolar disorder (BD) is a mood disorder characterized by cycling episodes of mania or hypomania and depression and has a 1% lifetime prevalence in the United States.<sup>167,180</sup> BD arises from a complex pathophysiology, including disturbances in neuroinflammation, prefrontal and limbic network activity, and neurotransmitter signaling.<sup>181,182</sup> First-line treatments include mood stabilizers and antipsychotics.<sup>183</sup> However, many patients remain symptomatic with response rates around 50% for acute episodes and lower rates for maintenance and bipolar depression, highlighting the limited treatment options for refractory cases.<sup>184</sup> SRS represents an underexplored treatment avenue for treatment-resistant BD. Preliminary studies suggest potential therapeutic relevance through targeted modulation of neural circuits. One investigation utilized non-ablative SRS of 75 Gy targeting the subgenual cingulate cortex in treatment-resistant bipolar depression.<sup>185</sup> Two of 3 patients achieved a clinically significant response at the 6-month point, but their recoveries were complicated by discrete stressful circumstances. Nevertheless, these data suggest that radiosurgical modulation of dysfunctional circuits in BD may offer therapeutic benefits. These patients should only be considered for SRS in the context of a carefully vetted clinical trial.

### Major Depressive Disorder

Major depressive disorder (MDD) is a heterogeneous mood disorder defined by at least 2 weeks of depressed mood or anhedonia accompanied by additional symptoms, such as sleep disturbances or suicide ideation.<sup>167,186</sup> Affecting approximately 20% of United States adults, MDD is a leading cause of disability and incurs a high societal burden due to its chronic, recurrent course.<sup>187-189</sup> While its neurobiology remains an area of active investigation, MDD has been associated with dysregulated neurotransmitter signaling, neuroplasticity, and structural and functional changes in multiple cortical and subcortical regions.<sup>190-195</sup> Psychotherapy and monoamine reuptake inhibitors, such as selective serotonin reuptake inhibitors, are the first-line treatments.<sup>196</sup> As the estimated prevalence of treatment-resistant depression is

30%, there is a critical need for novel therapeutic approaches.<sup>197</sup>

Mirroring OCD, SRS for treatment-resistant MDD has been reported for several targets. SRS with 140 Gy has recently been used to target the bilateral anterior limb of the internal capsule in 3 patients with depression.<sup>198</sup> Their depression had been present for over 50 years, and they had active suicidal ideation and were refractory to multiple medications and alternative therapy. Patients 1 and 2 improved from moderate depression scores to no depression and mild depression, respectively. Patient 3 similarly experienced reduced depressive symptoms, as she improved from moderately severe depression to moderate depression. In another study, SRS of 120 Gy was delivered to the anterior cingulate cortex in 5 patients with treatment-resistant MDD.<sup>199</sup> Overall, their depression symptoms improved by 65% at 24 months post-SRS. In a case report, a patient with a 30-year history of treatment-resistant depression and multiple suicide attempts was treated with SRS of 130 Gy targeted to the subcaudate region.<sup>200</sup> The patient's depression went into sustained remission beginning at 4 months post-SRS and continuing to 32 months, and antidepressant medications were discontinued. Importantly, no adverse effects, such as neurological or cognitive deficits, were noted in any of the 9 patients across the 3 studies. Together, these studies show promising outcomes in a small sample size and merit further investigation. As above, SRS remains an investigational treatment only for patients with MDD and must be evaluated alongside other methods of neuromodulation.

## Eating Disorders

Eating disorders (EDs) are psychiatric conditions characterized by persistent disturbances in eating patterns and associated emotions. The primary forms include anorexia nervosa, bulimia nervosa, and binge-eating disorder.<sup>201</sup> Lifetime prevalence for all types of EDs is approximately 2%, with a higher rate in females.<sup>202</sup> ED pathophysiology reflects a whole-body disorder characterized by metabolic, endocrine, and neurobiological changes.<sup>203,204</sup> Treatment guidelines for EDs highlight outpatient psychological therapies as first-line interventions, with more severe cases involving nutritional interventions, antidepressant or antipsychotic pharmacotherapy, and multimodal day- and inpatient treatments.<sup>205</sup> Despite these evidence-based approaches, recovery rates remain suboptimal, with 20%-30% of anorexia nervosa and bulimia nervosa patients developing treatment-refractory conditions, driving the need for novel therapeutic interventions.<sup>206</sup>

Emerging evidence suggests that targeted neurosurgical and radiotherapeutic approaches may offer promising avenues for treating severe, treatment-resistant anorexia nervosa. Other neuroablative procedures, such as radiofrequency ablation targeted to the anterior limb of the internal capsule and the anterior cingulate cortex, have demonstrated potential clinical utility.<sup>207-209</sup> However, non-invasive approaches using ionizing radiation have received minimal research attention. A single study of 6 patients with treatment-

refractory anorexia nervosa underwent SRS targeted to the bilateral anterior limb of the internal capsule.<sup>199</sup> A mean 40% increase in body mass index 6 months post-SRS was recorded, with sustained weight improvements during the available follow-up. Complementing this, another study demonstrated that progressive ablation of the right caudate nucleus in minipigs using combined SRS led to early changes in eating-related behaviors, including motivation and hedonism, with MRI confirming precise, localized effects.<sup>210</sup> These findings align with advances in stereotactic imaging and treatment planning, which enable high-precision targeting of appetite-regulating regions.<sup>211</sup> These studies agree on the therapeutic potential of targeting neural circuits implicated in anorexia pathophysiology as viable radiosurgical targets for refractory cases.

## Substance Use Disorders/Addiction

Substance use disorders, also referred to as drug addictions, are conditions of repeated misuse of a substance to the detriment of health and function.<sup>167</sup> The prevalence of all substance use disorders is estimated to be up to 30%, led by alcohol use disorder at 20% and other drug use disorders at 10%.<sup>212,213</sup> Substance use disorder neurobiology reflects a complex pathophysiological process and results in the dysregulation of the reward pathway. First-line treatment options depend on the specific substance, but pharmacotherapy (if available) combined with psychosocial interventions is the mainstay. Relapse rates are also variable. Studies of patients with opioid use disorder commonly determine a 50% or greater relapse risk within 6 months, with similar rates for alcohol use disorder at follow-up periods of several years.<sup>214-217</sup> New therapeutic modalities are urgently needed to serve these patients better.

In recent decades, neuromodulation has been applied using multiple approaches, such as DBS and radiofrequency ablation.<sup>218</sup> However, the radiofrequency ablation studies were discontinued due to questionable efficacy and poor safety standards.<sup>219-221</sup> Non-invasive modalities, such as transcranial magnetic stimulation targeting the dorsolateral prefrontal cortex and recently low-intensity focused ultrasound targeting the nucleus accumbens, a key node in the reward pathway, are currently in the early stages of clinical trials.<sup>218</sup> Radiosurgery has recently been proposed as another alternative. In a preclinical study, a rat model of alcohol use disorder received SRS with 100 Gy to the nucleus accumbens and showed promising improvements in alcohol preference.<sup>222</sup> Future work in radiosurgery is likely to build on these studies.

## Aggression

Aggression, behavior intended to harm others or oneself, can manifest in multiple conditions, including schizophrenia, BD, traumatic brain injury, and intellectual disability, requiring specialized intervention when severe.<sup>223</sup> Aggression is hypothesized to result from the loss of top-down inhibition of the prefrontal cortex over limbic structures, such as the amygdala.<sup>224</sup> Standard treatments combine antipsychotics

with cognitive-behavioral therapy.<sup>225</sup> Acute management typically employs antipsychotics and/or benzodiazepines in combination, though these agents show only small-to-moderate effect sizes for aggression reduction long-term.<sup>226-229</sup>

To date, most research studies on neuromodulation for aggression have focused on other brain stimulation techniques, such as DBS and radiofrequency ablation, for modulating activity in subcortical structures, including the amygdala and nucleus accumbens.<sup>230,231</sup> The capacity of these modalities to reduce unprovoked aggression and enhance impulse control underscores the therapeutic potential of a non-invasive and permanent method like radiosurgery. A study investigated SRS as a follow-up therapy after radiofrequency ablation in 3 patients with autism spectrum disorder with aggressive tendencies.<sup>232</sup> The amygdala was targeted with 24 Gy prescribed to the 50% isodose line, and the anterior cingulate cortex was treated with a maximum dose of 120 Gy. In all 3 patients, aggression scores decreased. These findings collectively suggest that while radiosurgical neuromodulation for aggression is still in its infancy, existing evidence from radiosurgical and other studies supports its further investigation as a next-generation intervention.

## Anxiety

Anxiety disorders are a group of conditions characterized by disproportionate levels of fear, anxiety, or avoidance.<sup>233</sup> Together, they are estimated to have a lifetime prevalence of 34%, with higher rates in women than men, and are frequently comorbid with other medical and psychiatric conditions, such as OCD.<sup>168</sup> Multiple brain systems are implicated in anxiety pathophysiology, including the dysfunctional negative valence circuit, which promotes fear generalization via excessive reactivity of the amygdala and impaired top-down inhibition from the prefrontal cortex.<sup>234</sup> First-line therapies include monoamine reuptake inhibitors and cognitive behavioral therapy, but between 35% and 55% of patients do not respond, creating an opportunity for alternative treatments.<sup>233,235</sup>

Radiofrequency ablation capsulotomy has been studied as a treatment for patients with severe, life-limiting, and medically refractory anxiety disorders, with preliminary studies showing efficacy but also a high incidence of frontal lobe syndrome, which is marked by disinhibition, apathy, and impaired executive functioning.<sup>236</sup> However, radiation therapy has not received the same interest. One study involved 7 patients who underwent bilateral SRS capsulotomy with a dose of 120-160 Gy. Five of the 7 patients' anxiety scores improved to a satisfactory degree.<sup>237</sup> In a follow-up study of 11 patients, clinical efficacy criteria were not clearly defined, and the authors noted a high incidence of adverse effects.<sup>238</sup> As in the radiofrequency ablation study, frontal lobe syndrome was observed, and headaches were reported as well. An additional study of ten patients from a separate group treated patients who had multiple psychiatric disorders, but the study was criticized for its lack of rigor in methodology and data reporting.<sup>239-241</sup> As in psychiatric conditions in general, the challenges of treating anxiety disorders with a

focal method like radiosurgery may be due to its complex pathophysiology.

## Future Directions

Psychosurgery began on dubious grounds nearly a century ago, based on the physiological and anatomical knowledge and surgical techniques of the time. Subsequent decades of biomedical research have advanced our understanding of disease pathology and informed the development of safer, more effective therapies, with modern ethics emphasizing patient autonomy, informed consent, and equitable access to care. However, significant gaps remain for patients with intractable psychiatric disorders. SRS may offer an alternative treatment for some of these patients, pairing the advantages of a non-invasive procedure with stereotactic accuracy. Now guided by connectomics-based imaging approaches, the patient-specific target brain region can be deep within the brain, where the inputs of a neural circuit frequently converge onto a node. Modulation of these nodes can then alter the dynamics of the greater circuit and influence behavior. The dose may be tailored to suit the clinical context, as lower doses can be used for tuning neural activity and higher doses for ablation.<sup>242</sup> However, the limited sample sizes and preliminary nature of existing data underscore the need for larger, controlled studies to establish definitive efficacy and comprehensive safety profiles before clinical implementation can be recommended.

## Conclusion

Radiation therapy, and SRS in particular, is a cornerstone in the management of numerous non-malignant central nervous system diseases. This review highlights its current use for treating patients with vestibular schwannomas, AVMs, TN, and ET. These indications are well-established. There is the potential of applying radiation therapy to treat patients with various psychiatric conditions, and even for those with AD. The advancement of these approaches will continue to be based on sound basic and clinical science, and work to date provides us with great optimism regarding these innovative uses of radiation therapy to benefit many patients around the world.

## Data availability

No new data were used for the research described in the article.

## Conflict of Interest

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