CyberKnife Robotic Stereotactic Radiosurgery

Erqi Pollom, Lei Wang, Iris C. Gibbs, and Scott G. Soltys

Introduction

The CyberKnife® (Accuray, Sunnyvale, CA, USA), conceived and developed by Dr. John Adler, a neurosurgeon at Stanford, treated its first patient in 1994. This pioneering radiosurgical system, the first that did not require a stereotactic frame, consists of a linear accelerator mounted on a robotic treatment delivery system that allows for six degrees of freedom, coupled to an image-guided targeting system. Intrafraction image guidance allows for submillimeter accuracy for both intracranial and extracranial body treatments.

As the first dedicated radiosurgical system capable of extracranial radiosurgery or stereotactic body radiotherapy, early trials explored the use of stereotactic principles, developed for intracranial radiosurgery, for treatment in the body. Among the earliest reports of body radiosurgery are series of patients treated with the CyberKnife for tumors of the spine, lung, pancreas, prostate, and liver. The early pioneering studies continue with recent reports of CyberKnife treatment for cardiac arrhythmia, ocular melanoma, and functional disorders.

We review the early history of the development of the CyberKnife, describe the components of the system that allow for stereotactic accuracy, highlight how advances in the technology over the years have contributed to clinical outcomes, and look to where the CyberKnife, and the field of radiosurgery, may be headed in the future.

History

Stereotactic radiosurgery (SRS) was conceived by Swedish neurosurgeon Dr. Lars Leksell in 1951 [1] and initially relied on rigid fixation of the skull by a stereotactic head frame used as reference in order to precisely target radiation beams to intracranial lesions. A frame-based approach had limitations which included patient discomfort and inability to deliver multi-session treatments. American neurosurgeon Dr. John Adler was inspired to develop a frameless radiosurgical device after a neurosurgical fellowship with Dr. Leksell at the Karolinska Institute in Stockholm in 1985 [2]. He believed that frameless targeting could be achieved through X-ray image-to-image correlation and that this type of image-guided radiosurgery would obviate the need for an invasive stereotactic frame. In addition to greater patient comfort, a frameless system would allow for fractionated treatment over several days while maintaining stereotactic accuracy, as well as extracranial radiosurgery.

When Dr. Adler accepted a position at Stanford in 1987, he set out to build the first frameless radiosurgical system with collaborators, former Varian and Stanford linear accelerator engineers, from Schomberg Engineering. His original concept, as described in a series of technical papers in the 1990s, described a linear accelerator mounted on a robotic arm to precisely deliver multiple non-isocentric and noncoplanar treatment beams with near real-time X-ray image guidance [3–7]. He founded Accuray, Inc. (Sunnyvale, Calif., USA) in 1990 to develop and manufacture the CyberKnife system.

The first CyberKnife prototype, initially called the Neurotron 1000, was installed and treated patients at Stanford University Medical Center between 1994 and 2000. On June 8, 1994, the first patient was treated, an elderly woman with a solitary brain metastasis. CyberKnife was approved by the United States Food and Drug Administration for intracranial applications in 1999, and then received clearance in 2001 for radiosurgical treatment of lesions anywhere in the body where radiation is indicated.

E. Pollom · L. Wang · I. C. Gibbs · S. G. Soltys (✉)
Stanford Cancer Institute, Stanford, CA, USA

Stanford University, Department of Radiation Oncology, Stanford, CA, USA
e-mail: sgsoltys@stanford.edu

D. M. Trifiletti et al. (eds.), *Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy*,
https://doi.org/10.1007/978-3-030-16924-4_6

Since the initial CyberKnife prototype, there have been five subsequent models through 2017. The second generation CyberKnife in 2001 introduced a new robot system (Kuka Roboter GmbH, Augsburg, Germany) and replaced the fluoroscopic screen/charge-coupled device camera with high resolution flat-panel amorphous silicon detectors. In 2002, the G3 model was introduced with more advanced image-tracking algorithms: six-degree skull tracking (6D Skull Tracking), fiducial-free spine tracking (XSight® Spine Tracking, Accuray, Sunnyvale, CA, USA), and Synchrony® (Accuray, Sunnyvale, CA, USA) for dynamic tracking on moving targets. Advances in imaging tracking techniques significantly improved delivery accuracy [8]. The G4 model was introduced in 2005 with an automated exchange table for the beam collimators. With the VSI model in 2009, improvements included a 6D Robot Couch, floor mounted high resolution (1024 × 1024) amorphous silicon detectors, higher dose rate (1000 monitor unite/minutes), the IRIS™ (Accuray, Sunnyvale, CA, USA) variable aperture collimator system, and fiducial-less lung tracking with Synchrony. The combination of high dose rate delivery and IRIS™ collimator significantly improved the delivery efficiency with the VSI system.

Improvements have led to the M6 model in 2012 with a new robot and a new room layout for a better robot working space. One significant advance of the M6 is multi-leaf colli-

Fig. 1 Representative models of the CyberKnife® (Accuray, Sunnyvale, CA, USA) system. (**a**) CyberKnife G3 system (2002). (**b**) CyberKnife G4 system (2005). (**c**) CyberKnife VSI system (2009). (**d**) CyberKnife M6 system (2012). (All images courtesy of Accuray Incorporated. © 2019 Accuray Incorporated. All rights reserved)

mator (MLC) capabilities which can improve treatment efficiency and expand the capability for larger treatment targets (Fig. 1a–d). In addition to hardware, advances in software optimization, segmentation, dose calculation, and beam/time reduction techniques have also been made over the years to the treatment planning system from the original On Target system to MultiPlan® system in 2005 to the most recent Precision™ system in 2017. Monte Carlo calculation was implemented in both MultiPlan and Precision planning system for more accurate dose calculations.

Given that the CyberKnife was frameless, radiosurgical treatment outside of the brain was soon explored. Some of the earliest reports of spine and body radiosurgery, also termed stereotactic body radiotherapy (SBRT), were performed with the CyberKnife. For lung cancer, among the first prospective trials was a phase I dose escalation trial of single-fraction SBRT using the CyberKnife, with doses up to 30 Gy in one fraction [9, 10]. A recent analysis of a national CyberKnife registry reported excellent outcomes on 723 patients with early-stage lung cancer treated with SRS/SBRT [11].

The CyberKnife was involved in the earliest reports of SBRT for treatment of primary and metastatic tumors of the liver. After a case report in 2006 on one patient treated to 36 Gy in three fractions [12], subsequent series of patients treated to higher doses of 30 Gy in one fraction or 46 Gy in five fractions noted good tumor control outcomes; reports in 2016 found 2-year local control of 82% in 115 patients [13] and 91% in 132 patients [14].

Similarly, prospective trials of CyberKnife pancreas SBRT noted early promise of the technique. First reported in 15 patients in a phase I dose escalation trial in 2004 [15], these early treatments often consisted of a breath-hold technique to manage intrafraction respiratory motion, with treatment up to 3 hours not uncommon. Subsequent phase II data reported local control of 94% in 19 patients treated with 45 Gy conventionally fractionated treatment followed by a 25 Gy SBRT boost [16]. Based on these experiences, a prospective, multi-institutional trial was conducted of SBRT to 33 Gy in five fractions with concurrent gemcitabine and reported slightly lower local control of 78% but acceptable rates of late gastrointestinal toxicities [17].

Prostate SBRT has become a standard of care for treatment of prostate cancer. Early pioneering studies investigated a homogeneous dose distribution [18] comparable to standard fractionated radiotherapy. Many large, single-institution series of nearly 500 patients with prostate cancer [19] treated with CyberKnife SBRT have subsequently been reported using the fractionation scheme of 35–40 Gy in five fractions and show promising tumor control and quality of life outcomes [20], similar to a later pooled, multi-institutional registry analysis of 2000 patients [21]. An alternative five-fraction protocol to emulate the heterogeneous dosimetry of high-dose rate (HDR) brachytherapy has also reported excellent prospective outcomes, suggesting that "Virtual HDR" CyberKnife SBRT may be a noninvasive alternative to brachytherapy for treating prostate cancer [22].

For head and neck malignancies, early data explored a CyberKnife radiosurgical boost to improve local control of nasopharyngeal carcinoma [23]. A prospective trial determined the maximum tolerated dose of five-fraction radiosurgery for recurrent head and neck carcinoma [24]; another prospective trial analyzed results of a six-fraction regimen [25]. Despite the precise dose delivery and highly conformal dose distribution CyberKnife allows in the re-irradiation setting, a large series of 381 patients reported the risks of carotid body blow-out with repeat CyberKnife irradiation for recurrent head and neck tumors [26], highlighting the importance of patient selection.

Although the basic concept that Dr. Adler created has remained unchanged over time, significant developments of the CyberKnife system have led to improvements in treatment planning, treatment delivery accuracy, treatment time, and range of body regions and indications that can technically be treated.

Recent Advances

The CyberKnife is a robotic treatment delivery system coupled to an image-guided targeting system. The treatment delivery system is composed of a lightweight, compact 6 MV X-band linear accelerator mounted to a robotic manipulator with six degrees of freedom. The image-guided targeting system consists of paired X-ray imaging sources and amorphous silicon flat panel detectors mounted on either side of the patient. Orthogonal images are obtained repeatedly throughout treatment and compared to digitally reconstructed radiographs (DRRs) derived from the pretreatment CT by aligning to bony anatomy or implanted fiducials. The treatment couch and robotic manipulator are then adjusted to resolve translational and rotational offsets between the orthogonal images and DRRs, allowing precise targeting of the LINAC. The overall system accuracy for intracranial targets of this frameless system with intrafraction motion management is less than 1 mm, similar to frame-based systems. A study on anthropomorphic head phantoms found targeting accuracy of approximately 0.5 mm [27].

While intracranial accuracy relies on skull tracking, early CyberKnife software did not allow for bone tracking of extracranial sites. The initial CyberKnife spinal radiosurgery procedures required placement of metal fiducial markers within the adjacent vertebral body, an open surgical procedure prior to spinal SRS [28]. While 6D skull tracking allows for treatment delivery to intracranial targets, XSight™ (Accuray, Sunnyvale, CA, USA) is a modification of the CyberKnife system that allows accurate tracking anywhere within or adjacent to spine. As with skull tracking, image registration with the XSight spine tracking system is based on high contrast bone data. A 9

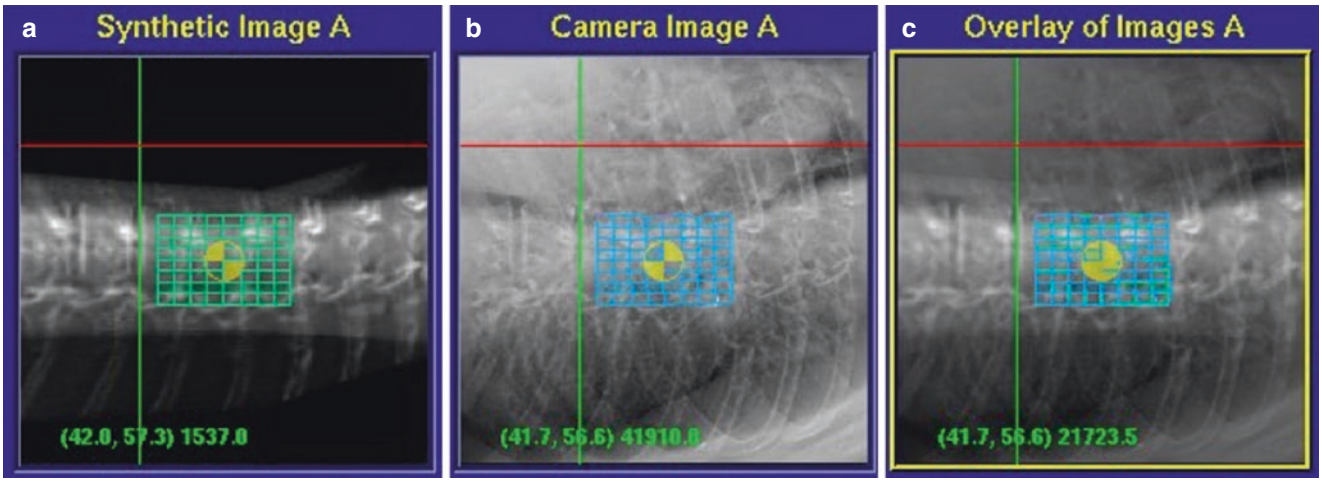

Fig. 2 Fiducial-less tracking of the spine by the XSight® (Accuray, Sunnyvale, CA, USA) spine software for intrafraction motion management. In (**a**), a 9 × 9 deformable grid, each intersecting point acting as a fiducial, is overlaid onto the digitally reconstructed radiograph (DRR). In (**b**), the patient's live radiograph is shown; notice the deformation of the tracking grid to match the patient's position. (**c**) is a fused image of (**a**) and (**b**) as a summary view. (All images courtesy of Accuray Incorporated. © 2019 Accuray Incorporated. All rights reserved)

by 9 grid of 81 nodes, each of which fulfills the role of a virtual fiducial, is displayed over each of the two orthogonal DRRs (Fig. 2a–c). The grid size can be adjusted to maximize the number of nodes containing bony anatomy. A matching algorithm then computes local displacement vectors for each node between images acquired during treatment and the original DRR and computes a final translation and rotation vector used to register the patient. This system can accurately target spinal lesions with submillimeter accuracy without spine-implanted fiducials [29].

With frameless image guidance technology came the ability to perform body radiosurgery. Similar to the early experience of spinal radiosurgery, the treatment of body sites required implantation of fiducials. To account for intrafraction motion management due to respiratory motion, these pioneering early treatments utilized deep-inspiration breath-hold techniques, stopping treatment delivery between breaths, and often would take up to 3 hours. Innovations in motion tracking and treatment delivery led to the Synchrony™ (Accuray, Sunnyvale, CA, USA) system. This image-guided system allows targeting of tumors that move with respiration in the thorax or abdomen. Unlike respiratory gating, where the beam position is fixed, turning on for a fraction of the respiratory cycle to deliver dose when the tumor is within position, Synchrony utilizes respiratory tracking, where the entire beam position moves with the tumor, treating it during the entire respiratory cycle. This system separately images light-emitting diodes (LEDs) placed on the chest wall to track respiratory movement as well as radiopaque fiducial markers placed within or near the tumor. The movement of the LEDs on the chest wall is correlated with internal movement of the fiducials [30]. Based on both data sets, a predictive model is generated and updated throughout the treatment based on changes in the patient's breathing pattern (Fig. 3a, b). The accuracy of Synchrony has been demonstrated even for irregular motion patterns and phase shifts between external chest and internal tumor motion [31, 32]. Software advances led to Xsight™ Lung which, in conjunction with Synchrony respiratory tracking system, allows for some lung tumors to be tracked directly, without implanted fiducials [33]. This approach uses direct soft tissue tracking rather than invasive fiducial insertion and requires sufficient tumor size and contrast against surrounding lung tissue in X-ray images, typically peripheral or apical lung regions, larger than 15 mm, and distant from the spine.

In 2012, the CyberKnife M6 series was released followed by the addition of a micro-multileaf collimator (InCise™ MLC, Accuray, Sunnyvale, CA, USA) in 2014 [34]. The InCise™ MLC allowed delivery of irregularly shaped fields, thus using fewer beams and lower total monitor units compared with non-isocentric fixed or IRIS™ variable aperture collimated fields. The major advantage of MLC is treatment time reduction. Compared to cone-based plan, an average of 30–35% time and MU reduction are reported. MLC plans have the potential of achieving a better dose gradient at the low-dose region [35, 36] as investigated in liver [37], intra-

cranial, and prostate targets [38]. The second version of InCise™ MLC has leaf width of 3.8 mm at 80 cm source to target distance with maximum field size of 100 mm by 115 mm at 80 cm from source.

Furthermore, the robotic mounting of the CyberKnife linac allows for non-isocentric treatment planning, a significant departure from most other radiosurgical systems that utilize isocentric sphere packing techniques, isocentric coplanar volumetric modulated arcs, or isocentric noncoplanar arcs. While high-dose regions of the treatment plans are similar among different techniques, a noncoplanar, non-isocentric plan may allow for a steeper gradient of low dose, particularly for body and spinal SRS plans [39].

a

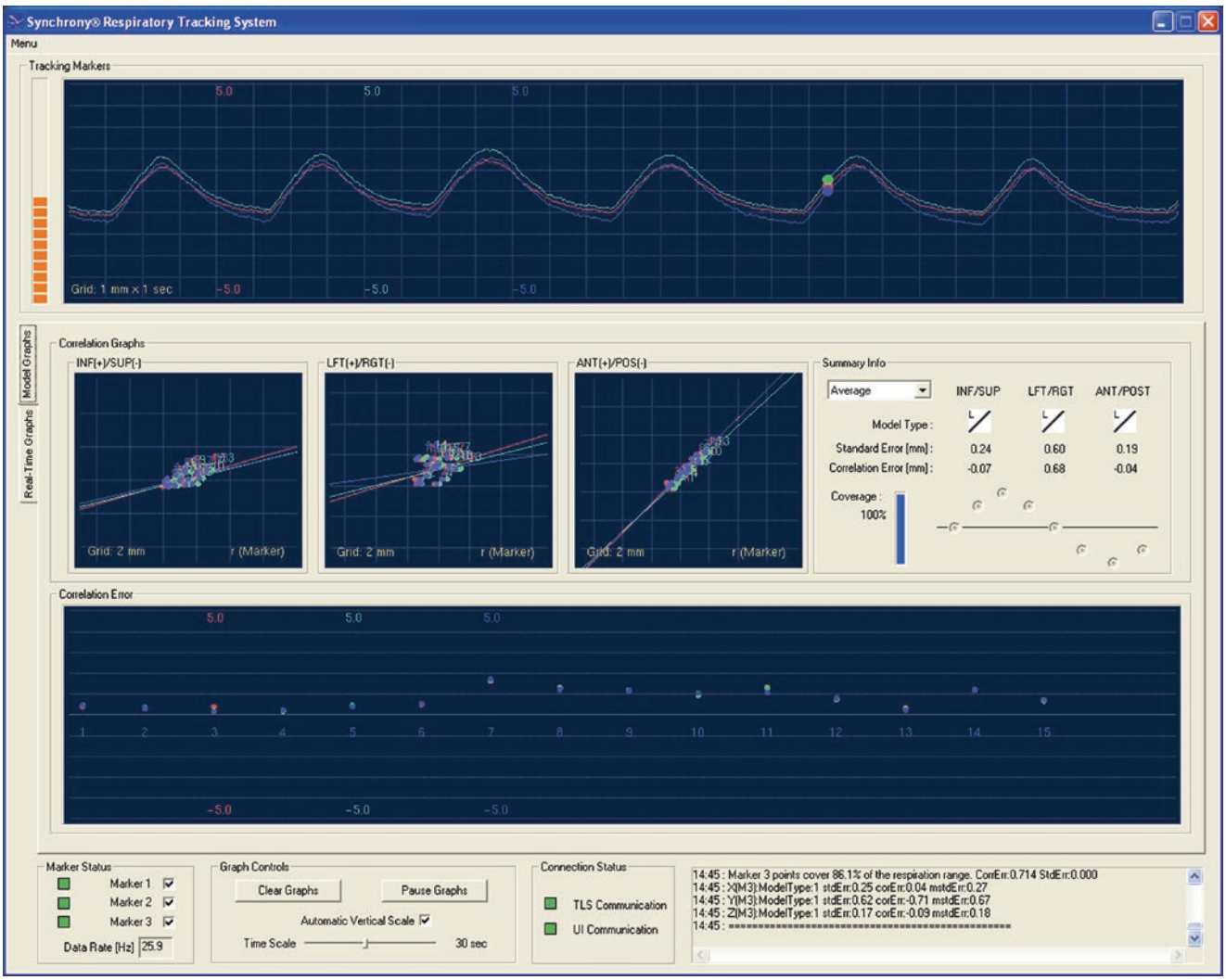

Fig. 3 A Synchrony® (Accuray, Sunnyvale, CA, USA) tracking screen for management of respiratory motion. The respiratory cycle trace from externally placed light-emitting diode (LED) (**a**) is correlated with the position of fiducials internally implanted into the tumor (the correlation model of the external LED and internal fiducial is shown in the middle panel). The total treatment correlation error accounted for in the treatment is shown in (**b**). (All images courtesy of Accuray Incorporated. © 2019 Accuray Incorporated. All rights reserved)

b

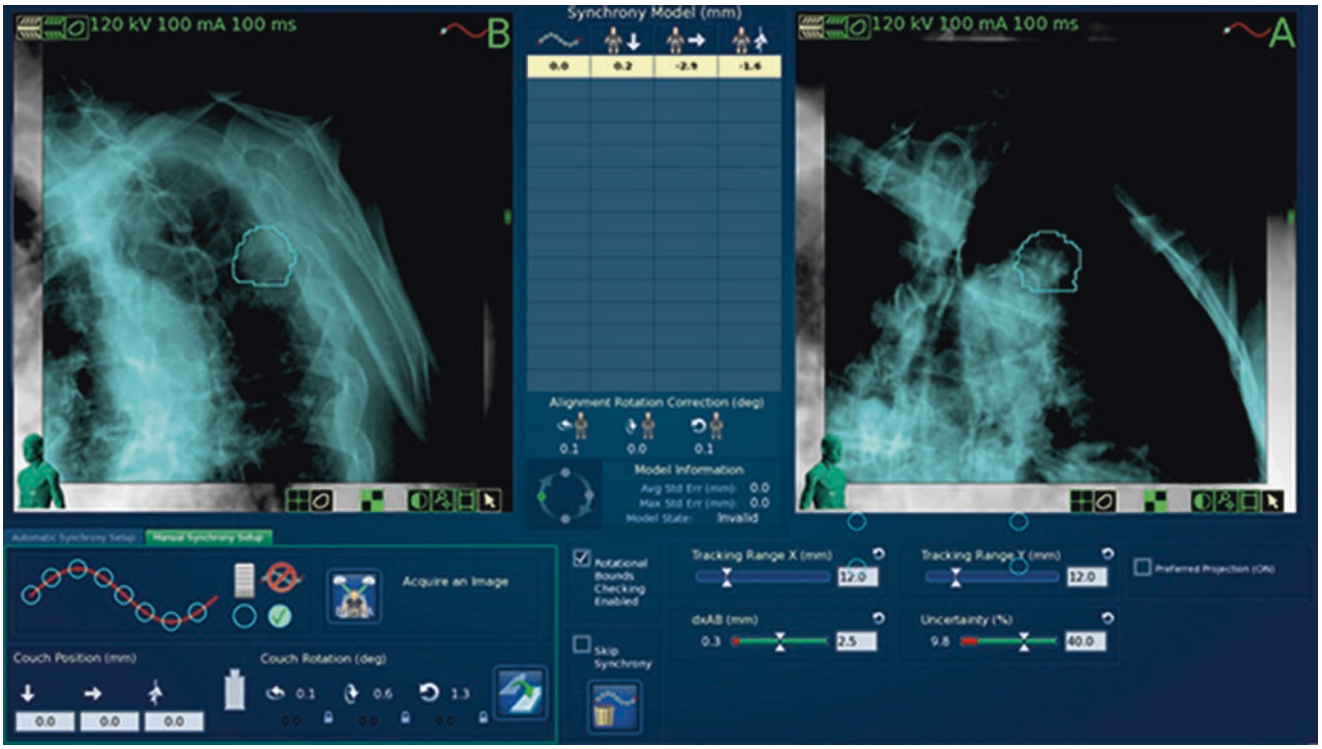

Fig. 3 (continued)

Limitations

The dose rate of earlier CyberKnife models was 300 MU/minute. It has been increased to 600–1000 MU/minute for the G4 and VSI models, and 1000MU/minute for the M6. In addition to increased dose rate, the treatment times of the newer models are improved over older models due to a time reduction function during treatment planning, the IRIS™ variable collimator and MLC capabilities. The treatment time for a typical intracranial plan with current CyberKnife technology (VSI and M6) is about 25–30 minutes compared to 45–60 minutes on earlier models. However, due to the step and shoot method used with CyberKnife and the significant robot travel time between delivery nodes, treatment efficiency is still the major drawback compared to the continuous arc delivery on linac-based systems, where a plan can be delivered within 5 minutes. Better optimization techniques and continuous delivery method are required to further reduce treatment times.

The CyberKnife delivers dose at predesignated node positions with most of the beams coming from an anterior oblique direction. Posterior beams are restricted to avoid collision of linac head with the ground. Compared to VSI and earlier models, the M6 model has the robot aligned at the head of the treatment couch instead of to the right or left superior corner of the couch. The M6 treatment space is now symmetric laterally and allows many more posterior oblique beams, up to 20 degrees below horizontal. Despite this improvement, the limited posterior beams is a weakness of the system and introduces more dose anteriorly, the clinical relevance of this relatively low dose spill is uncertain [40].

The current CyberKnife imaging guidance system provides great speed and low imaging dose [41–43], but the lack of volumetric imaging is a potential drawback compared with cone beam CT imaging guidance on other linac systems. Additionally, although the smaller beamlets used in CyberKnife provide steep gradients, they also result in higher MUs compared to linac arc plans, which introduces higher peripheral dose and leakage dose to the patients. This higher body dose is of unknown clinical significance.

For the functional disorder trigeminal neuralgia, the non-isocentric treatment of a length of the trigeminal nerve is a standard of care [44], distinct from the isocentric approach of GammaKnife. However, the treatment of functional targets other than trigeminal neuralgia with the CyberKnife system can be challenging. Past and current versions of SRS treatment planning software have not allowed multi-planar rotation of the native CT and MR images. Although case series of functional treatments exist [45, 46], this lack of image rotation makes targeting of cranial targets for ablation (e.g., thalamotomy for movement disorders, capsulotomies for obsessive compulsive disorders) difficult, as the coordi-

nates are based on a coplanar view of the anterior commissure-posterior commissure (AC-PC) line. Targeting via brain atlas coordinates often requires target identification with external software, then importation of that target into the CyberKnife system for SRS planning. Furthermore, the greater lateral penumbra from the higher energy 6MV photons of the CyberKnife leads to a less steep low-dose gradient than for lower energy photons such as the average 1.25 MV photons from cobalt sources. Whether this inherently greater low dose region has clinical implications is unknown.

Overall, further studies are required to compare not only effectiveness of competing technologies but also costs and impact on patient quality of life.

Future Directions

CyberKnife radiosurgery has been increasingly used as a noninvasive method to treat malignant and benign conditions, both intracranially as well as extracranially. This technology has also shown promise in a number of diseases not previously treated with radiotherapy. Conditions traditionally treated with thermal ablation, which causes injury through heating and coagulation, can be targeted for ablation through radioablation with high dose radiotherapy. For example, the first-in-human radiosurgical ablation of the heart to treat a cardiac arrhythmia [47] was performed with the CyberKnife. A later series of patients treated with noninvasive stereotactic radioablation which targeted the arrhythmogenic area of the heart found a reduction in the burden of refractory ventricular tachycardia [48]. CyberKnife treatment has shown potential in treating other cardiovascular condition such as nephrogenic hypertension, where a reduction in norepinephrine was seen following radiosurgical injury of the renal nerve in porcine models [49].

Lars Leksell first described Gamma Knife to create highly focused lesions in the brain to treat a variety of pain syndromes and movement disorders. The most common functional disorder for CyberKnife radiosurgery has been trigeminal neuralgia [44]. Radiosurgery for trigeminal neuralgia appears to work through partial axonal injury and degeneration at doses of 80 Gy [50]. The remaining intact axon population is usually sufficient to maintain facial sensation. Interest has naturally extended to explore these principles of decreasing pain conductibility while maintaining sensation and function for extracranial pain syndromes. Specifically, spinal SRS could potentially be used to treat chronic pain syndromes, as shown in a proof-of-principle experiment using Yucatan minipigs treated with a 90 Gy single dose of radiation targeting a small volume of spinal nerve [51]. The authors found that targeted nerves had a 65% loss of both large and small myelinated fibers and unmyelinated fibers associated with focal collagen deposition. The sections of the dorsal root ganglia demonstrated intact ganglia, satellite cells, and myelinated and unmyelinated nerve fibers leading into and out of the ganglia. The authors concluded that it is possible to irradiate spinal nerves, causing partial nerve fiber degeneration and possibly decreasing conductibility through the nerve but not completely abolishing function. Such treatment requires high levels of imaging and targeting accuracy, which have been made possible with improvements in spinal radiosurgery with the CyberKnife treatment system.

CyberKnife radiosurgery has also been used to perform a rhizotomy of the nerves innervating the spinal facet joint in five patients with facetogenic back pain [52]. Three of the five patients experienced pain improvement within one month of radiation treatment with a median follow-up of 10 months. No patient experienced acute or late-onset toxicity.

Although CyberKnife radiosurgery for uveal melanoma is a standard treatment in the Herzog Carl Theodor Eye Hospital in Munich, Germany, its use elsewhere in the world has not been widely reported and is a potential area of growth for any radiosurgery program. The initial paper of this approach described 20 patients treated with the process of retrobulbar anesthesia followed by SRS planning and delivery of a median dose of 20 Gy in one fraction, all within 3 hours while the eye is immobilized [53]. Localization during treatment delivery can be achieved by either retrobulbar anesthesia for eye immobilization [54–56] or a camera system to monitor eye motion [57]. The latest report note good outcomes for this high risk population, with 5 year local control of 71% in 217 patients [56] with similar quality of life compared to those treated with enucleation [58].

Although SBRT is a standard of care in the spine, lung, liver, pancreas, and prostate, less data are noted for renal radiosurgery, another indication for potential growth in the field of stereotactic body radiotherapy. The first CyberKnife renal SBRT report consisted of a single patient treated to 25 Gy in one fraction in 2010 [59]. The latest reports show local tumor control rate of 93% with doses up to 48 Gy in three fractions [60].

Looking forward, the future of CyberKnife and the field of radiosurgery and stereotactic body radiotherapy as a whole relies on identifying new conditions where radiation is not currently an indication. For example, the recent high-profile report on cardiac radiosurgery for ablation of arrhythmia [48] will likely lead to further research to optimize and expand this indication. Similarly, our field should look to areas where thermal ablation is a current treatment and explore comparative outcomes of noninvasive ablation with irradiation. These areas may include SRS for facetogenic back pain [52], thalamotomy for movement disorder or capsulotomy for obsessive compulsive disease rather than thermal ablation [61, 62], and renal artery hypertension [49] and

neuromodulation (rather than neuro-ablation) for psychiatric disorders [63]. Additionally, as reported above, the overall trend in radiation oncology is to pursue hypofractionated treatment as opposed to traditional fractionation to shorten treatment times, improve toxicity and quality of life, and potentially improve outcomes. The goal of hypofractionation is slowly being explored in neuro-oncology [64] but is still not the standard of care. We await expansion and maturation of early reports showing promising outcomes of primary radiosurgery for chordoma [65] as opposed to 8 weeks of traditionally fractionated radiotherapy, for newly diagnosed glioblastoma [66, 67], shorter than the standard 6 weeks of radiotherapy, and eagerly await future reports of new indications for radiosurgery.

Practical Considerations

Patient Setup

- Ensure comfortable patient position as treatment times can take up to an hour
- For brain lesions, a thermoplastic head mask with head rest is used
- For cervical spine lesions, a longer mask is used to stabilize head and neck
- For thoracic/lumbar spine and thoracic/abdominal/pelvic lesions, a vacuum bag is used for immobilization
- CT scan is performed using 1–1.5 mm slices (for higher-resolution DRRs and better tracking accuracy), centered on target extending 10–15 cm above and below the target, and encompassing organs at risk
- The primary CT used for treatment planning should be non-contrasted as contrast may distort DRR quality and impact tracking accuracy

Target Definition and Treatment Planning

- CT image acquired at simulation is used for dose calculation during treatment planning and for generating DRRs used for setup and tracking during treatment delivery.
- Can import MRI, PET, and additional CT scans into the Treatment Planning System (TPS) to register with primary CT image to aid in target delineation.
- Treatment plans are generated using one of three optimization methods: isocentric, conformal, or sequential optimization. Treatment plans should be optimized on critical structure constraints, plan conformity, and dose gradient.
- Given the multiple non-isocentric, noncoplanar beams of irradiation, one may pay attention to dose delivered outside of the axial plane of the target for extracranial targets.

Treatment Delivery

- A pair of orthogonal KV X-ray sources and detectors allow for accurate target localization and near real-time tracking using bony landmarks (for intracranial or spine lesions) or fiducial markers (usually for prostate, lung, liver)
- On initial setup, visual examination of the alignment between the live images and the DRRs is essential. The alignment is approved by a physician before treatment starts. Standard radiosurgery safety procedures should be followed
- During the treatment, images should be taken every 15–150 seconds, depending on treatment site and patient motion stability

References

1. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand. 1951;102:316–9.
2. Adler JR. Accruray, incorporated: a neurosurgical business case study. Clin Neurosurg. 2005;52:87.
3. Adler JR Jr, Chang SD, Murphy MJ, Doty J, Geis P, Hancock SL. The Cyberknife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg. 1997;69(1–4 Pt 2):124–8.
4. Adler JR Jr, Murphy MJ, Chang SD, Hancock SL. Image-guided robotic radiosurgery. Neurosurgery. 1999;44(6):1299–306; discussion 1306–7
5. Murphy MJ, Cox RS. The accuracy of dose localization for an image-guided frameless radiosurgery system. Med Phys. 1996;23(12):2043–9.
6. Murphy MJ. An automatic six-degree-of-freedom image registration algorithm for image-guided frameless stereotaxic radiosurgery. Med Phys. 1997;24(6):857–66.
7. Schweikard A, Bodduluri M, Adler JR. Planning for camera-guided robotic radiosurgery. IEEE Trans Rob Autom. 1998;14(6):951–62.
8. Fu D, Kuduvalli G. A fast, accurate, and automatic 2D-3D image registration for image-guided cranial radiosurgery. Med Phys. 2008;35(5):2180–94.
9. Whyte RI, Crownover R, Murphy MJ, Martin DP, Rice TW, DeCamp MM Jr, et al. Stereotactic radiosurgery for lung tumors: preliminary report of a phase I trial. Ann Thorac Surg. 2003;75(4):1097–101.
10. Le Q-T, Loo BW, Ho A, Cotrutz C, Koong AC, Wakelee H, et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. J Thorac Oncol. 2006;1(8):802–9.
11. Davis JN, Medbery C 3rd, Sharma S, Perry D, Pablo J, D'Ambrosio DJ, et al. Stereotactic body radiotherapy for early-stage non-small cell lung cancer: clinical outcomes from a National Patient Registry. J Radiat Oncol. 2015;4(1):55–63.
12. Chung YW, Han DS, Paik CH, Kim JP, Choi JH, Sohn JH, et al. Localized esophageal ulcerations after CyberKnife treatment for metastatic hepatic tumor of colon cancer. Korean J Gastroenterol. 2006;47(6):449–53.
13. Que J, Kuo H-T, Lin L-C, Lin K-L, Lin C-H, Lin Y-W, et al. Clinical outcomes and prognostic factors of cyberknife stereotactic body radiation therapy for unresectable hepatocellular carcinoma. BMC Cancer. 2016;16:451.
14. Su T-S, Liang P, Lu H-Z, Liang J, Gao Y-C, Zhou Y, et al. Stereotactic body radiation therapy for small primary or recurrent

hepatocellular carcinoma in 132 Chinese patients. J Surg Oncol. 2016;113(2):181–7.
15. Koong AC, Le QT, Ho A, Fong B, Fisher G, Cho C, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;58(4):1017–21.
16. Koong AC, Christofferson E, Le QT, Goodman KA, Ho A, Kuo T, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2005;63(2):320–3.
17. Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015;121(7):1128–37.
18. King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti JC Jr. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. Int J Radiat Oncol Biol Phys. 2009;73(4):1043–8.
19. Katz AJ, Kang J. Stereotactic body radiotherapy as treatment for organ confined low- and intermediate-risk prostate carcinoma, a 7-year study. Front Oncol. 2014;4:240.
20. Katz AJ, Kang J. Quality of life and toxicity after SBRT for organ-confined prostate cancer, a 7-year study. Front Oncol. 2014;4:301.
21. Freeman D, Dickerson G, Perman M. Multi-institutional registry for prostate cancer radiosurgery: a prospective observational clinical trial. Front Oncol. 2014;4:369.
22. Fuller DB, Naitoh J, Mardirossian G. Virtual HDR CyberKnife SBRT for localized prostatic carcinoma: 5-year disease-free survival and toxicity observations. Front Oncol. 2014;24(4):321.
23. Le Q-T, Tate D, Koong A, Gibbs IC, Chang SD, Adler JR, et al. Improved local control with stereotactic radiosurgical boost in patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2003;56(4):1046–54.
24. Heron DE, Ferris RL, Karamouzis M, Andrade RS, Deeb EL, Burton S, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. Int J Radiat Oncol Biol Phys. 2009;75(5):1493–500.
25. Lartigau EF, Tresch E, Thariat J, Graff P, Coche-Dequeant B, Benezery K, et al. Multi institutional phase II study of concomitant stereotactic reirradiation and cetuximab for recurrent head and neck cancer. Radiother Oncol. 2013;109(2):281–5.
26. Yamazaki H, Ogita M, Kodani N, Nakamura S, Inoue H, Himei K, et al. Frequency, outcome and prognostic factors of carotid blowout syndrome after hypofractionated re-irradiation of head and neck cancer using CyberKnife: a multi-institutional study. Radiother Oncol. 2013;107(3):305–9.
27. Antypas C, Pantelis E. Performance evaluation of a CyberKnife G4 image-guided robotic stereotactic radiosurgery system. Phys Med Biol. 2008;53(17):4697–718.
28. Ryu SI, Chang SD, Kim DH, Murphy MJ, Le QT, Martin DP, et al. Image-guided hypo-fractionated stereotactic radiosurgery to spinal lesions. Neurosurgery. 2001;49(4):838–46.
29. Ho AK, Fu D, Cotrutz C, Hancock SL, Chang SD, Gibbs IC, et al. A study of the accuracy of cyberknife spinal radiosurgery using skeletal structure tracking. Neurosurgery. 2007;60(2 Suppl 1):ONS147–56; discussion ONS156.
30. Schweikard A, Shiomi H, Adler J. Respiration tracking in radiosurgery. Med Phys. 2004;31(10):2738–41.
31. Pepin EW, Wu H, Zhang Y, Lord B. Correlation and prediction uncertainties in the cyberknife synchrony respiratory tracking system. Med Phys. 2011;38(7):4036–44.
32. Nioutsikou E, Seppenwoolde Y, Symonds-Tayler JRN, Heijmen B, Evans P, Webb S. Dosimetric investigation of lung tumor motion compensation with a robotic respiratory tracking system: an experimental study. Med Phys. 2008;35(4):1232–40.
33. Urschel HC. Robotic radiosurgery. Treating tumors that move with respiration. Springer-Verlag Berlin Heidelberg: Springer Science & Business Media; 2007. 317 p.
34. Fürweger C, Prins P, Coskan H, Heijmen BJM. Characteristics and performance of the first commercial multileaf collimator for a robotic radiosurgery system. Med Phys. 2016;43(5):2063.
35. van de Water S, Hoogeman MS, Breedveld S, Nuyttens JJME, Schaart DR, Heijmen BJM. Variable circular collimator in robotic radiosurgery: a time-efficient alternative to a mini-multileaf collimator? Int J Radiat Oncol Biol Phys. 2011;81(3):863–70.
36. McGuinness CM, Gottschalk AR, Lessard E, Nakamura JL, Pinnaduwage D, Pouliot J, et al. Investigating the clinical advantages of a robotic linac equipped with a multileaf collimator in the treatment of brain and prostate cancer patients. J Appl Clin Med Phys. 2015;16(5):284–95.
37. Jin L, Price RA, Wang L, Meyer J, Fan JJ, Ma C, et al. Dosimetric and delivery efficiency investigation for treating hepatic lesions with a MLC-equipped robotic radiosurgery--radiotherapy combined system. Med Phys. 2016;43(2):727–33.
38. Kathriarachchi V, Shang C, Evans G, Leventouri T, Kalantzis G. Dosimetric and radiobiological comparison of CyberKnife M6™ InCise multileaf collimator over IRIS™ variable collimator in prostate stereotactic body radiation therapy. J Med Phys. 2016;41(2):135–43.
39. Nalichowski A, Kaufman I, Gallo J, Bossenberger T, Solberg T, Ramirez E, et al. Single fraction radiosurgery/stereotactic body radiation therapy (SBRT) for spine metastasis: a dosimetric comparison of multiple delivery platforms. J Appl Clin Med Phys. 2017;18(1):164–9.
40. Fürweger C, Drexler C, Muacevic A, Wowra B, de Klerck EC, Hoogeman MS. CyberKnife robotic spinal radiosurgery in prone position: dosimetric advantage due to posterior radiation access? J Appl Clin Med Phys. 2014;15(4):4427.
41. Chuang CF, Larson DA, Zytkovicz A, Smith V, Petti PL. Peripheral dose measurement for CyberKnife radiosurgery with upgraded linac shielding. Med Phys. 2008;35(4):1494–6.
42. Murphy MJ, Balter J, Balter S, BenComo JA Jr, Das IJ, Jiang SB, et al. The management of imaging dose during image-guided radiotherapy: report of the AAPM Task Group 75. Med Phys. 2007;34(10):4041–63.
43. Petti PL, Chuang CF, Smith V, Larson DA. Peripheral doses in CyberKnife radiosurgery. Med Phys. 2006;33(6):1770–9.
44. Adler JR Jr, Bower R, Gupta G, Lim M, Efron A, Gibbs IC, et al. Nonisocentric radiosurgical rhizotomy for trigeminal neuralgia. Neurosurgery. 2009;64(2 Suppl):A84–90.
45. Stancanello J, Romanelli P, Pantelis E, Sebastiano F, Modugno N. Atlas-based functional radiosurgery: early results. Med Phys. 2009;36(2):457–63.
46. Franzini A, Marchetti M, Brait L, Milanesi I, Messina G, Forapani E, et al. Deep brain stimulation and frameless stereotactic radiosurgery in the treatment of bilateral parkinsonian tremor: target selection and case report of two patients. Acta Neurochir. 2011;153(5):1069–75.
47. Loo BW Jr, Soltys SG, Wang L, Lo A, Fahimian BP, Iagaru A, et al. Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. Circ Arrhythm Electrophysiol. 2015;8(3):748–50.
48. Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. N Engl J Med. 2017;377(24):2325–36.
49. Bhatt N, Long SA, Gardner EA, Tay J, Ladich E, Chamberlain D, et al. Radiosurgical ablation of the renal nerve in a porcine model: a minimally invasive therapeutic approach to treat refractory hypertension. Cureus. 2017;9(2):e1055.
50. Kondziolka D, Lacomis D, Niranjan A, Mori Y, Maesawa S, Fellows W, et al. Histological effects of trigeminal nerve radiosurgery in a

primate model: implications for trigeminal neuralgia radiosurgery. Neurosurgery. 2000;46(4):971–6. discussion 976–7.
51. De Salles AAF, Medin P. Functional spine radiosurgery. Spine Radiosurgery. 2009;1:176.
52. Li G, Patil C, Adler JR, Lad SP, Soltys SG, Gibbs IC, et al. CyberKnife rhizotomy for facetogenic back pain: a pilot study. Neurosurg Focus. 2007;23(6):E2.
53. Muacevic A, Nentwich M, Wowra B, Staerk S, Kampik A, Schaller U. Development of a streamlined, non-invasive robotic radiosurgery method for treatment of uveal melanoma. Technol Cancer Res Treat. 2008;7(5):369–74.
54. Klingenstein A, Fürweger C, Nentwich MM, Schaller UC, Foerster PI, Wowra B, et al. Quality of life in the follow-up of uveal melanoma patients after CyberKnife treatment. Melanoma Res. 2013;23(6):481–8.
55. Zorlu F, Selek U, Kiratli H. Initial results of fractionated CyberKnife radiosurgery for uveal melanoma. J Neuro-Oncol. 2009;94(1):111–7.
56. Eibl-Lindner K, Fürweger C, Nentwich M, Foerster P, Wowra B, Schaller U, et al. Robotic radiosurgery for the treatment of medium and large uveal melanoma. Melanoma Res. 2016;26(1):51–7.
57. Béliveau-Nadeau D, Callejo S, Roberge D. Technique for robotic stereotactic irradiation of choroidal melanoma. Cureus. 2016;8(4):e582.
58. Klingenstein A, Fürweger C, Mühlhofer AK, Leicht SF, Schaller UC, Muacevic A, et al. Quality of life in the follow-up of uveal melanoma patients after enucleation in comparison to CyberKnife treatment. Graefes Arch Clin Exp Ophthalmol. 2016;254(5):1005–12.
59. Staehler M, Fürweger C, Kufeld M, Karl A, Roosen A, Stief C, et al. Cyberknife radiosurgery of a renal pelvis tumor to avoid renal dialysis. Cureus [Internet]. 2010;Cureus 2(11):e17. https://doi.org/10.7759/cureus.17.
60. Sun MRM, Brook A, Powell MF, Kaliannan K, Wagner AA, Kaplan ID, et al. Effect of stereotactic body radiotherapy on the growth kinetics and enhancement pattern of primary renal tumors. AJR Am J Roentgenol. 2016;206(3):544–53.
61. Witjas T, Carron R, Krack P, Eusebio A, Vaugoyeau M, Hariz M, et al. A prospective single-blind study of gamma knife thalamotomy for tremor. Neurology. 2015;85(18):1562–8.
62. Kondziolka D, Flickinger JC, Hudak R. Results following gamma knife radiosurgical anterior capsulotomies for obsessive compulsive disorder. Neurosurgery. 2011;68(1):28–32; discussion 23–3
63. Borchers DJ, Litchfield CP, Schaal DW, Adler JR. Stereotactic Radiosurgical Neuromodulation for chemical dependency: a theoretical approach to addiction therapy. Cureus. 2009;Cureus 1(12):e6. https://doi.org/10.7759/cureus.6.
64. Shah JL, Li G, Shaffer JL, Azoulay MI, Gibbs IC, Nagpal S, et al. Stereotactic radiosurgery and hypofractionated radiotherapy for glioblastoma. Neurosurgery. 2018;82(1):24–34.
65. Yamada Y, Laufer I, Cox BW, Lovelock DM, Maki RG, Zatcky JM, et al. Preliminary results of high-dose single-fraction radiotherapy for the management of chordomas of the spine and sacrum. Neurosurgery. 2013;73(4):673–80; discussion 680
66. Pollom EL, Fujimoto D, Wynne J, Seiger K, Modlin LA, Jacobs LR, et al. Phase 1/2 trial of 5-fraction stereotactic radiosurgery with 5-mm margins with concurrent and adjuvant Temozolomide in newly diagnosed Supratentorial glioblastoma: health-related quality of life results. Int J Radiat Oncol Biol Phys. 2017;98(1):123–30.
67. Ney DE, Carlson JA, Damek DM, Gaspar LE, Kavanagh BD, Kleinschmidt-DeMasters BK, et al. Phase II trial of hypofractionated intensity-modulated radiation therapy combined with temozolomide and bevacizumab for patients with newly diagnosed glioblastoma. J Neuro-Oncol. 2015;122(1):135–43.