The CyberKnife in Clinical Use: Current Roles, Future Expectations

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Abstract
The CyberKnife system deploys a linac mounted on an agile robot and directed under image guidance for stereotactic radiotherapy using nonisocentric beam delivery. A design advantage of the CyberKnife system is its method of active image guidance during treatment delivery. Recent developments in the hardware and software of the system have significantly enhanced its functionality: (a) an optimized path traversal process significantly reduces the robot motion time, resulting in reductions of overall treatment times of at least 5–10 min; (b) to optimize the accuracy of dose calculation in CyberKnife planning/delivery, Monte Carlo algorithms have been introduced; (c) the new IRIS collimator reduces the monitor units required, increases treatment speed and improves conformality and homogeneity of treatment plans; (d) X-Sight lung tracking, an algorithm for fiducial-less lung tracking, has been developed for peripheral, radio-dense lung tumors with diameters >15 mm; and (e) a sequential optimization planning process incorporates a more flexible approach to optimize the multiple, complex treatment planning criteria used today. The clinical efficacy of CyberKnife radiosurgery for brain/head lesions such as metastases, arteriovenous malformations, acoustic neuromas and meningiomas is well established. Since there is no need for skeletal fixation with the CyberKnife, radiosurgery can be applied to targets beyond the brain, and the technology has been extensively used for stereotactic body radiotherapy, treating targets in many anatomic sites. Currently, clinical studies have been completed or are ongoing for common malignancies including tumors involving the spine, lung, pancreas, liver and prostate.

The CyberKnife System

The CyberKnife was developed in the 1990s at Stanford, where 2 systems are now operational. Last year over 700 patients were treated, and the Stanford clinic now has cumulative experience with over 5,000 patients. The CyberKnife (Accuray Inc., Sunnyvale, Calif., USA) consists of a 6-MV, flattening-filter free linac mounted on an industrial robot (Kuka, Augsburg, Germany) [1]. The patient couch may
be conventional or robotic. An X-ray imaging system, consisting of 2 cameras in the ceiling directed obliquely toward amorphous silicon detectors integrated into the floor, is installed in the treatment room. This imaging system is used for 2D-3D image registration [2–5] of the live images to a digitally reconstructed radiograph, which determines the patient position in near real-time and is used to correct for patient motion during treatment. The accuracy of the system is defined by the end-to-end test. This test takes a phantom through the complete treatment planning and delivery process, comparing the location of the delivered 70% isodose with the planned dose. In our experience and in the literature, the observed accuracy ranges from 0.4 to 0.7 mm [3].

A design advantage of the CyberKnife system is its method of active image guidance during treatment delivery. The system is capable of imaging before every treatment beam. However, as several authors have shown [6–9], imaging can be skipped for a small number of beams (e.g. every 3–5 beams) to reduce imaging dose without compromising dose delivery accuracy. Generally, imaging every third to fifth beam or every 20 to 60 s, depending on the compliance of the patient, is sufficient. Typical treatment times are about 20–30 min, and 1–5 fractions are delivered in each treatment course.

It is often thought that the CyberKnife is a stereotactic system and can treat only small tumors; however, the system is able to treat quite large tumors (up to 2,500 cm$^3$) if they are appropriately planned. The homogeneity of the treatment field is commonly cited in terms of prescribing to the 80% isodose line. Although many physicians prescribe in this manner, it is not a necessity. The treatment can be planned with whatever level of homogeneity requested, as this is a matter of prioritizing the constraints in the plan. This provides operative flexibility in the dosimetry that can be tailored to the clinical intent. For instance, it is possible to create plans mimicking Gamma Knife treatment by using a 50% prescription isodose line resulting in large inhomogeneity. Another example of purposely utilizing inhomogeneous plans is to replicate the dose distribution of an HDR treatment [10]. On the other hand, more homogeneous plans (with only 10–13% inhomogeneity) can be designed for prostate treatments equally well [11].

The CyberKnife represents a major paradigm shift from traditional stereotactic radiosurgery (SRS) technology. The prior SRS delivery systems have employed a fixed gantry with isocentric beam delivery, whereby the radiation dose is given relative to a central point of focus. Dose conformity is achieved by ‘sphere packing’, a treatment planning technique that creates multiple spherical or ellipsoid dose distributions. The CyberKnife uses an agile robot that is capable of delivering dose at any point within the target. This nonisocentric beam delivery allows optimal dose conformity without compromising dose homogeneity.

Additionally, since there is no need for skeletal fixation with the CyberKnife, radiosurgery can be applied to targets beyond the brain. Currently, clinical studies
have been completed or are ongoing for common malignancies including tumors involving the spine, lung, pancreas, liver and prostate. In this chapter we review the current roles and future expectations of the CyberKnife system, and provide practical guidelines for its clinical use.

**Advances in CyberKnife Treatment Planning and Dose Delivery**

Recent developments in hardware and software have significantly enhanced the CyberKnife’s functionality from the basic system described above. We will highlight some of these new technical developments and their useful applications for treatment.

**Optimized Path Traversal**

The CyberKnife was the first robotic device in which a human was permitted to be present within a robot workspace. As safety precautions, the FDA implemented regulations limiting the speed of the robot motion and requiring its travel to occur only along a set of predefined paths, stopping at treatment ‘nodes’ (fig. 1). At each stopping position, the robot could change the linac beam angle within limits to create 12 beam directions at each node. In the initial design, the robot sequentially travelled to all nodes whether or not treatment monitor units were assigned to them by the treatment plan, which added to the overall treatment time.

*Fig. 1. Left side: treatment nodes located around the patient. Right side: 12 beam directions originating from a node. Figure courtesy of Accuray Inc.*
After a decade of experience with patient safety and operational reliability of the Kuka robot, federal regulations have been updated. Optimized path traversal is now approved, which reduces the total treatment pathway and improves delivery time while still maintaining safety requirements. How does the optimized path traversal system work?

A complete path set contains about 120 nodes, but most treatment plans use only a subset of them. For each plan, the system creates a matrix of the travel paths from each node to all subsequent nodes being used in the plan. There is also an ‘obstacle file’ that contains all areas in space which the robot cannot cross, e.g. the couch or the patient safety zone. Based on the obstacle file, all routes which cross an obstacle are eliminated, leaving only the list of safe routes between nodes. Figure 2 shows a robot path designed to move around obstacles projected onto a 2D surface. For instance, if nodes 7 and 8 have no beams with dose, the robot may move directly from node 6 to 9, but only if a safe route exists. Otherwise, a node cannot be skipped, and nodes may be included in the path only for safety reasons. Overall, the robot now traverses the shortest safe distance between nodes with dose. In addition, if one needs to interrupt treatment for any reason, treatment can resume at the point of interruption by skipping nodes already used for treatment and moving to the starting point of the make-up treatment. This optimized path traversal process significantly reduces robot motion time, resulting in reductions of overall treatment times of at least 5–10 min, depending on the level of pre-existing planning efficiency.

Monte Carlo Dose Calculation Algorithm

The ability of algorithms to accurately model dose perturbations in regions of tissue inhomogeneity has been a long-standing problem in medical physics. Simple dose calculation models such as the ray-tracing algorithm, which was initially the only algorithm implemented in the CyberKnife planning system, were known to work very well in homogeneous areas of the body such as the brain. It was also known that such a pencil beam-based algorithm, which uses a simplistic density correction model for inhomogeneities, does not model in vivo dose distributions very well in inhomogeneous areas such as the lung. Further, these inaccuracies become increasingly pronounced in small lesions and treatment fields as used in stereotactic work. Not unique to the CyberKnife, these issues exist for all treatment planning systems for stereotactic delivery that use these older dose calculation algorithms.

To improve the accuracy of dose calculation in CyberKnife planning/delivery, Monte Carlo (MC) algorithms have been available for the fixed collimators since 2008, and for the IRIS collimator since 2009. The MC calculation is based on a
dual-source model of the CyberKnife photon beam using the EGS4/BEAM MC code [12, 13].

1. To create the MC model, 3 beam parameters need to be measured: (a) the in-air output factor for an open collimator, (b) the open field profile and (c) the percent depth dose for the 60-mm collimator.

2. The linac source model is then created from the data. Cone correction factors and energy correction factors are used as parameters to iteratively fit the MC-generated tissue-phantom ratio and off-center ratio to the measured beam data.

3. After those fits are completed, the MC-based output factors are calculated and compared with measured output factors.

4. Clinical commissioning of the MC model is completed by verifying the accuracy of the delivered dose distribution by measurement in an inhomogeneous phantom [14, 15].

In the clinical application, the first plan remains always a pencil beam calculation. The user then can recalculate the pencil beam dose distribution with MC leaving the initial beam directions and monitor units/beam constant. Depending on the desired dose uncertainty, this recalculation will take 5–20 min. If the resulting dose distribution differs significantly from the pencil beam calculation, the user can either change the prescription isodose line or reoptimize the plan using MC. In the current clinical implementation, the first step is to calculate a ray-tracing plan, followed by a recalculation with MC to assess the difference between both plans. The planner then has the option to either use this recalculated plan and adjust the dose prescription accordingly, or reoptimize the plan with MC. Reoptimization is a good option if the beam weighting can be changed so that more beams enter from more homogeneous directions of the patient’s body. In the case of a lung lesion in the middle of the lung, where dose differences originate from the change of build-up dose and scatter dose at the interface between the tissues, reoptimization with MC will not result in signifi-

Fig. 2. Concept of optimized path traversal. A robot path designed to travel from node to node around obstacles (shaded areas) is projected onto a 2D space. Safe paths that skip nodes (green arrow) and unsafe paths (red arrow) are mapped. See online supplementary material.
cant improvement. The physical situation in this case will require a lower prescription isodose line, i.e. larger inhomogeneity to cover the target adequately. Wilcox et al. [16] have shown the ratio of maximum dose in a lung tumor to change between 1.0 (no change) and 1.7 (a 70% change). The exact change is highly dependent on tumor location and size and has to be assessed on a patient-by-patient basis. Current clinical studies such as RTOG 0613 incorporate improved methods for inhomogeneity correction in the dose calculation requirements and will provide the data to adjust dose prescriptions based on older studies such as RTOG 0236 [17].

Other sites often showing inhomogeneity are the thoracic spine (because of proximity to lung tissue), nasopharynx and embolized AVM lesions. By default, these areas and other potential areas of concern should be recalculated with MC to assess how much the inhomogeneities influence the dose distributions. Especially for SRS, one should consider a shift of the isodose line due to the accuracy of the dose calculation on an equivalent level as the spatial dose delivery accuracy.

Before any new dose calculation algorithm such as MC is clinically implemented, the accuracy of the dose calculation must be verified clinically by measurement in a phantom. Since the algorithm requires input parameters that are based on measurements and a model that is adjusted during the commissioning process to match the beam data of a specific machine, each institution must repeat the quality assurance process of dose calculation verification measurements. Published data have shown a high degree of accuracy when using a well-implemented MC dose calculation algorithm [14, 15].

**IRIS Collimator**

Since the early development of the CyberKnife, the option of adding a mini-multileaf collimator to it has been discussed (though peer-reviewed studies on the advantage of a multileaf have not been published yet). The use of multiple collimators can reduce the monitor units and time needed to deliver a plan [18]. The IRIS collimator [19] was designed to maximize the utilization of multiple field sizes in CyberKnife radiosurgery (see online supplementary video).

The IRIS collimator has 2 collimator banks with 6 leaves each, rotated by 30 degrees relative to each other, thereby creating a near-circular field shape. The apertures are adjustable for each treatment beam from a 60- to 5-mm beam diameter with an aperture reproducibility of ±0.1 mm. In the current implementation, the beam diameters are incremental to match the fixed collimator set. In clinical practice, the IRIS collimator reduces the monitor units required, decreases treatment times and improves conformity and homogeneity of treatment plans.
Sequential Optimization

To take full advantage of the IRIS collimator, a new treatment planning algorithm called 'sequential optimization' (or 'stepwise optimization') was developed [20]. It incorporates a more flexible approach to optimize the multiple, complex treatment planning criteria used today. For example, the priority and tolerance levels on criteria such as conformality, target coverage, organ-at-risk sparing and homogeneity goals can vary considerably between patients based on their disease site, clinical history and other variables. The stepwise optimization process of sequential planning mimics closely the decision making process of the physician when designing a clinical treatment plan.

Contrary to a dose-volume histogram-based planning algorithm, where all criteria are optimized at once and priorities can only be set by relative weights, sequential optimization optimizes 1 criterion at a time in the order of priority, which the user has defined. In addition, the solution of each prior step is maintained, or relaxed by a user-defined value, when the next step is optimized. This method always maintains a feasible solution. The plan quality with respect to one criterion is never impaired in subsequent steps. The idea is to represent every clinical planning criterion as a constraint in an objective function. This method of sequential optimization lends itself to scripting: if a certain subgroup of patients is always planned with the same criteria, dosimetric variability due to differing level of treatment planning skills can be largely eliminated by scripting the plan optimization. It is also possible to quickly tailor the plan to preferences of individual physicians or to specific aspects of patients’ histories (e.g. irradiated vs. unirradiated spinal segments, which would have different objectives for the spinal cord).

Figure 3 shows an example of a sequential optimization script for a spine tumor abutting the spinal cord. In step 1, the tumor prescription dose of 24 Gy is set. The relaxation value of 10 Gy is larger than typical, but in this case, where the cord is immediately adjacent to the tumor, some underdosing of the tumor has to be accepted to maintain cord tolerance. Step 2 defines the maximum cord tolerance, 14 Gy, which cannot be compromised (hence the tolerance value of 0 Gy). In step 3, the tumor should be covered as homogeneously as possible. Step 4 uses an (asymmetric) tuning shell to optimize conformality. Right kidney sparing is achieved in step 5. Finally, step 6 optimizes (minimizes) the monitor units; the goal and relaxation values are nominal for this step.

Xsight Lung Tracking

Regardless of the technology, direct tracking of lung tumors requires implanted fiducials as surrogates to mark the position of radiographically low-contrast le-
sions. While the implant procedure is usually safe, with only minor and uncommon complications [21–23], it requires an investment in time, additional risk and added cost. Implanting fiducials is more challenging for more peripheral tumors. Can these markers be eliminated for some cases? XSight lung tracking [24], which is an algorithm for fiducial-less lung tracking, has been developed for peripheral, radio-dense lung tumors with diameters >15 mm.

For XSight lung tracking, the tumor GTV is contoured for treatment planning. This PTV contour is then used by the tracking algorithm to create a matching square in the oblique imaging projection bounding the tumor. The spine is segmented out to improve tracking accuracy. During the treatment, a pattern-similarity matching algorithm [25] is used to identify the tumor in the live X-ray images and compare the tumor position with the digitally reconstructed radiographs to localize it. This localization information is then processed in Synchrony respiratory tracking [26] in the same way as fiducial-based localization.

**Current Clinical Applications of CyberKnife**

**Brain, Base of Skull Tumors**

The clinical efficacy of radiosurgery for brain lesions such as metastases, arteriovenous malformations, acoustic neuromas and meningiomas is well established [27–31], and the CyberKnife can be used effectively for these lesions, similarly to
other radiosurgical machines. Additional flexibility of the CyberKnife platform has allowed for: (a) efficient treatment strategies employing fractionation with up to 5 fractions, which may benefit lesions adjacent to sensitive critical tissues such as cranial nerves or the spinal cord, and (b) treatment of more generous target sizes such as large meningiomas and brain metastatic resection cavities [32, 33].

In traditional single fraction radiosurgery, tumors that extend to within a few millimeters of the anterior optic nerve structures are generally not considered ideal candidates for therapy. However, using the CyberKnife, our group has treated such periop tic tumors, most commonly with doses of 18–25 Gy in up to 5 fractions. Our studies confirm visual preservation in 94% of subjects at a mean follow-up of 49 months [13].

In another application, we are testing the hypothesis that greater fractionation may increase hearing preservation after acoustic neuroma radiosurgery. The potential role of limited fractionation in achieving this goal is debated, and the ability to generate highly conformal and homogeneous dose distributions using the CyberKnife makes it feasible to explore this hypothesis. Using CyberKnife radiosurgery delivering a total dose of 18–21 Gy in 3 fractions, our treatment series of 61 patients now has at least 3 years of follow-up: 74% of patients have maintained serviceable hearing, no patient developed a new trigeminal nerve injury and local control was 98% with only 1 patient demonstrating progression [34].

In some cases, fractionation allows treatment of somewhat larger volumes than traditional single fraction radiosurgery. As a proof of concept, our group has treated patients following surgical resection of brain metastases with radiosurgery to the resection cavity, despite the larger treatment volumes than conventionally accepted for radiosurgery. Our recent series demonstrated similar rates of local tumor control within the resection site, as compared with whole brain radiotherapy but with more limited brain exposure. Our group is now exploring dose escalation for brain tumors or their resection cavities if 2–5 cm in size, to test the optimal dose for this strategy in a prospective trial; the beginning dose levels are 24–27 Gy in 3 fractions.

Spinal Tumors

Another growing application of radiosurgery is for spinal metastases and primary spine tumors. Many of the early investigations of image-guided spinal radiosurgery were performed using the CyberKnife. This includes one of the largest, a single institution series of 500 patients with spinal metastases reported by Gerszten et al [35]. Overall their rate of long-term pain improvement was 86% and clinical improvement was 84%. As other image-guided technologies begin to report similar rates of efficacy, several prospective trials are currently underway to compare pain control rates achieved by radiosurgery with other palliative approaches.
Lung Cancer

Owing to its frameless image-guidance platform, the CyberKnife has been most extensively used as a technology for stereotactic body radiotherapy (SBRT), treating targets within the spine, lung, abdomen and pelvis. With lung cancer representing one of the most common cancers, and emerging clinical data confirming that SBRT of primary early stage lung tumors is superior to the historical results of conventional radiotherapy, lung cancer is one of the most rapidly growing indications for CyberKnife SBRT.

While surgery remains the standard of care for operable patients, SBRT has emerged as a preferable treatment for medically inoperable patients. RTOG 0236 is a multicenter prospective phase II study of SBRT for peripherally located, non-metastatic stage T1–T3 lung tumors (chest wall invasion only, ≤5 cm in size) in medically inoperable patients. The trial specifies 60 Gy delivered in 3 fractions (equivalent to 54 Gy in 3 fractions when using more accurate dose calculation algorithms). Among 55 evaluable patients enrolled, the 3-year actuarial local control rate was 97.6% at a median follow-up time of 34.4 months. There have been 2 regional relapses, and distant metastasis has been the primary mode of progression in 11 patients [36]. This trial has established the general clinical use of SBRT for such patients. Currently, typical fractionation schedules range from single fraction treatments of approximately 30 Gy for small T1 lesions to multifraction regimens of 54 Gy in 3 fractions (established based on RTOG 0236) for peripheral lesions. Ongoing investigations seek to determine the optimal schedule for centrally located tumors. Given the promising results seen in medically inoperable patients, international randomized trials have been launched to compare surgery with SBRT for medically operable patients including a CyberKnife radiosurgery study (STARS trial) and the ROSEL trial [37].

GI, GU and Other Tumors

Clinical studies using CyberKnife have also demonstrated clinical feasibility and safety for pancreatic and liver tumors [38–41]. Additional trials are required to determine the optimal treatment schedules. Reports of CyberKnife for prostate cancer have begun to emerge that build upon 2 different basic study rationales. The first is the assumption that prostate cancer has a unique biology that favors large doses per fraction, and SBRT regimens have been devised and tested with encouraging early results [42–44]. Another approach simply mimics the dosimetry of high dose rate brachytherapy and tests the feasibility of using CyberKnife noninvasively to deliver similar dosimetry [10, 44]. Two ongoing clinical trials are studying each of these strategies using the CyberKnife radiosurgery system.
Image Guidance/Tracking

What are the new directions and opportunities for development of the CyberKnife system? The CyberKnife already has an excellent localization system, which is superior to many other approaches because of its regular imaging and tracking during treatment, not just for patient setup before treatment. Also, the 2D-3D tracking algorithms [2, 4, 5, 24] for correlating orthogonal X-ray pairs to a 3D CT study clearly have advantages: 2D-3D registration is fast, uses a low imaging dose and is excellent for localizing bone structures.

The system does not provide volumetric imaging. However, in hypofractionated treatments, there is less need for adaptive planning approaches because the tumor and other anatomy will not change much during the short courses of therapy. In the CNS and upper head-and-neck regions (e.g. nasopharynx), tumors and organs at risk are fixed relative to skeletal structures and not deforming, changing significantly or moving during the course of a SRS treatment. Why change the system?

Alternative approaches for the localization process could be important contributions to its targeting reliability and range of use. First, volumetric information would be very valuable for localizing soft tissue structures. Second, localization using nonionizing methods, including optical, ultrasound or radiofrequency beacon systems, would be desirable. Third, localization methods permitting prone treatments would expand the usability of the system.

One example in which 3D nonionizing tracking options could improve the system clinically is in respiratory motion tracking (Synchrony). The localization process for Synchrony uses a hybrid system with beacons on the skin monitoring overall respiratory motion and X-rays monitoring tumor targets (either using fiducials as surrogate markers or soft tissue tracking). To achieve accuracy of the treatment delivery, there must be accuracy of the correlation model between skin and tumor throughout all phases of respiration. But in some patients, a good correlation model is difficult to establish; the root cause for this has not been established yet. Irregularity of the respiratory motion itself, although often said to cause tracking inaccuracy, has not been shown to cause significant tracking inaccuracies [26]. Instead, the crux of the problem is the correlation (or lack of it) between the skin and tumor motion, which may change throughout treatment.

This issue is not unique to the CyberKnife system. Of note, we have learned that 4D CT is not necessarily a good predictor of motion at the time of treatment [45], which also indicates that the 4D CT may also not be a good predictor of the correlation model. In some cases, there can be significant differences which could be major concerns, especially for gated forms of treatment delivery.
In the clinical process of localization for Synchrony, an ideal design would involve some form of direct tumor tracking using nonionizing modalities. Possible approaches include: electromagnetic methods (such as the Calypso system using implanted beacons), ultrasound for some tumor sites, optical surface matching in combination with deformable registration or MR. One might even consider an approach using electromyography to use the nerve signal to the diaphragm, instead of the motion of the abdomen, as the surrogate marker for respiration.

New Clinical Applications

Recent publications report active research to expand the uses of noninvasive, frameless SRS systems such as the CyberKnife beyond cancer therapy applications [46]. Many ‘minimally invasive’ procedures such as radiofrequency ablation, deep-brain stimulation and others are being used for several benign conditions, but these procedures still carry risks of anesthesia complication and infection [47–49]. These are not shared by SRS, which is entirely noninvasive and could be studied as a potential option in these situations, especially for patients who would otherwise not be candidates for treatment.

References


