Key Points

- Stereotactic radiosurgery is the delivery of a highly-focused beam of radiation to a target
- It uses very high doses, but is highly conformal, so surrounding tissue toxicity is low
- Tumours treated successfully include brain, intra-nasal, osteosarcoma, bladder, prostate, urethra, heart-base, liver
- Treatments are typically delivered in 1-3 fractions with obvious benefits to the patient and client

Radiosurgery was originally defined as a single-fraction technique that used stereotactic principles for targeting and treatment of intracranial lesions through the use of multiple noncoplanar beams (SRS). Over the past two decades the stereotactic techniques on which radiosurgery are founded have been applied to fractionated treatments, termed stereotactic radiotherapy (SRT), and applications outside the skull, termed stereotactic body radiosurgery (SBRS) or stereotactic body radiotherapy (SBRT). Outlined below is the history of radiosurgery, the development of radiosurgery techniques, and specific radiosurgery challenges. An understanding of this evolution helps describe the development of a veterinary radiosurgery program at UF.

History of the linear accelerator

X-rays were used to treat skin cancer back in 1896, and x-rays and radium were both used by early neurosurgeons including Harvey Cushing. This progressed to the ‘radium bomb’ designed by Mallet-Coliez (1924) which was a 13-source radium device with all sources focused on a single point, used to treat head and neck cancer and brain tumours, arguably an early gamma knife.

The first linear accelerator (Linac) was invented in 1928 (Wideroe) and simply accelerated charged subatomic particles in a linear beam line by subjecting them to a series of oscillating electric potentials and was very low energy. William Hansen (1938) increased the energy by accelerating the electrons by passing them through a resonant microwave cavity (Rhumbatron). The ‘modern’ linear accelerator relies on Bremsstrahlung radiation, arising from microwave-accelerated electrons stopping in a heavy metal target (usually a tungsten alloy) producing photons which are then collimated and aimed at the patient. Versions of this were produced in Stamford (1948) and England (1953) but it was the invention of the isocentric LinAc (that rotates around a point which is always in focus) by Varian in 1960 that heralded a new age.

In parallel to the advent of targeted photon delivery, was the development of computers, stereotactic frames and modern medical imaging such as CT, MRI and PET-CT. These all combined in the 1950s to give birth to the radiosurgical era.

History of radiosurgery in human medicine

There are three ‘chapters’ of radiosurgery, namely the gamma knife, particle beams, and linear accelerator systems.

The Swedish neurosurgeon Lars Leksell is the recognized father of the gamma knife. His other accomplishments include discovering the gamma motor neuronal system (1945, PhD), designing the Leksell double-action rongeur, describing Leksell’s pallidotomy for Parkinson’s disease, and
creating the Leksell stereotactic frame (1948) – the prototype arc-centred frame design used
everywhere today. In 1951 along with Larsson he developed the radiosurgical concept and
coined the term. They used 200 kV x-rays for early treatments, moving to intersecting proton
beams in 1957 using the Uppsala University Cyclotron (termed Stralkniven – “ray knives”).
LinAcs were not considered at this time as they were not isocentric, nor accurate enough to
perform radiosurgery, hence the birth of the Gamma Knife. Using multiple cobalt 60 sources
(179 in early devices, 201 in the newest, e.g. “Leksell Perfexion” from Elektra) arranged in a
cone-shaped design, they deliver focused radiation from moving sources with internal
collimation.

Particle beam (proton) radiosurgery was suggested by Wilson in 1947. Photons from the Linac
or Gamma Knife exponentially decay as they pass through tissue, and the radiosurgical effect is
achieved by intersecting multiple photon beams. Protons from a Cyclotron however (helium
beams) demonstrate increased energy through tissue, which then abruptly stop, with zero exit
dose. The technology was first used in Berkeley to irradiate breast cancer metastases in the
pituitary in 1954 and in 1961 the Harvard Cyclotron Lab and Mass General Hospital collaborated
to provide proton radiosurgery and have since treated over 9000 patients. Many proton beam
centres are now available, including a UF facility in Jacksonville. Proton therapy reportedly
offers a higher chance of a cure for uveal melanoma, chondrosarcoma, chordoma and
unresectable sarcomas. It reportedly has decreased side-effects which is attractive for pediatric
neoplasms and potentially the prostate. It is expensive technology (approximately $150M to set-
up) and expansion is currently driven by the re-imbursement system.

Linear accelerator radiosurgery (Linac Scalpel) is the most recent development. The technology
of coupling a stereotactic system to a Linac was reported in 1985 by Colombo who attached a
stereotactic head frame to a patient, fixing an intracranial target to the rotational isocentre of a
4MV Linac. The radiation source and the patient are rotated so the target is irradiated through
infinite portals and multiple (5-10) intersecting 120-degree arcs distributed over the convexity
of the skull, creating a very high radiation dose centred into the target with a stepped dose gradient.
The arc angles are usually smaller than 180 degrees to avoid parallel-opposed beams in the plane
of the arc. Work in 1988 (Winston & Lutz) and 1989 (Friedman & Bova at UF) measured and
then improved the accuracy of the Linac, and Radionics produced the first commercial Linac
radiosurgery system in 1990. Veterinary radiosurgery programs have evolved around the Linac
Scalpel system, as upgrading existing Linacs with the necessary hardware and software to make
them radiosurgery ready is accomplished for one tenth the cost of the Gamma Knife.

Image-guidance radiotherapy (IGRT)

Once the technology existed to deliver high doses of conformal radiation to a target, the
next challenge was to identify the target in a patient and synchronise both planning and delivery.
The limiting factor was typically the inability to guarantee that the initial simulation of the target
(plan) could be replicated at the time of therapy (treatment). Radiosurgery overcame this obstacle
through the use of a rigidly fixed reference system in the form of a stereotactic frame. The frame
is attached to the patient’s skull and remains there throughout the diagnostic examinations
necessary (MRI/CT) to localize the target and then plan the treatment. Once a rigid geometrical
relationship between the reflective fiducials on the stereotactic frame and the tumour target have
been established, optical tracking devices can follow the fiducials and allow for reproducible,
reliable, and accurate positioning and delivery of treatment based on the simulation/plan.
Frameless stereotaxy aims to dispense with the stereotactic frame without losing the inherent accuracy of the frame-based technique. New techniques use on-board imaging (OBI) to position patients in a reproducible fashion, by either; cone-beam CT (Varian, Elektra, Siemens); or orthogonal x-rays of bony landmarks or implanted gold fiducials (Cyberknife).

The tomotherapy concept for delivering IGRT combines treatment planning, patient positioning and dose delivery in one system. A 6MV miniature Linac mounted on a CT-type gantry ring allows the Linac to rotate around the patient. Beam collimation is accomplished by a multi-leaf collimator also mounted on the gantry that modulates the radiation intensity as the Linac rotates around the patient.

Conformal radiosurgery through beam shaping; sphere packing and multi-leaf collimators

Linac and gamma knife radiosurgery has historically relied on circular collimators (cones) and spherical symmetrical dose delivery, resulting in tumour coverage through ‘sphere-packing’. Radiosurgery uses cones ranging from 5mm to 40mm and through a combination of circular collimators and varying sized isocentres, a composite radiation shape that closely matches the shape of a non-spherical lesion is achievable. Dose inhomogeneity is introduced however by the overlap of the spherical distributions, but this can be minimized by carefully spacing the spheres relative to one another. Through circular fields and multiple isocentres, in theory dose conformation can be achieved for any arbitrarily shaped target by packing small spheres into the target – the only practical limits are the patience of the treatment planning team and a conceptual grasp of the 3D shape.

Another approach is to use multiple fixed beams of radiation, or micro multi-leaf collimators (MLC), typically with 120 leaves, which allow for irregular uniform intensity fields. The shape of the MLC closely matches the shape of the lesion from that particular view and effectively treats the whole irregular target with a single isocentre. Advantages of the micro-MLC approach over the multiple isocentre approach include; improved dose homogeneity; sharper dose fall-off outside the target; less time-consuming treatment planning; shorter treatment time; and less scatter dose to the patient.

Respiratory motion

For lesions outside the skull, organ motion must be controlled and this is achieved through one of the following:
- dampening (breath holding, under anaesthetic)
- gating (organ is imaged when moving, and treatment is only delivered when the image is in a defined location)
- chasing (the motion of an organ is determined and an algorithm created that will follow the organ, aka beam-chasing)

The newest Linac Scalpel is the Varian Trilogy, containing patented UF software and hardware for radiosurgery. It uses optical guidance technology, on-board imaging (cone-beam CT), 120 micro-multileaf collimators, and real-time position management (RPM) for respiratory gating.

Veterinary Radiosurgery (SRS, SBRS) at the McKnight Brain Institute, UF (1999-2011)

Until 2011, the SRS program at the University of Florida College of Veterinary Medicine (UF-CVM) was co-ordinated through the McKnight Brain Institute (MBI), part of the Dept of Neurosurgery in the University of Florida College of Medicine. All treatments were delivered at the MBI. Treatments were a single fraction of radiation using collimating cones, to create a conformal target through sphere-packing. The image-guidance was through optical tracking.
hardware and software, using a rigidly-applied external fiducial array to provide stereotaxis. The diagnostic imaging (CT/MRI) was performed at the UF-CVM with the fiducial array attached, and then the patient either treated immediately under the same anaesthetic (having been transported anaesthetized across town), or else anaesthetized at a later date and the array re-attached. The fiducial array was attached to a bite-plate and two techniques developed for array fixation:

- Dental arcade; for tumours of the skull (brain/sino-nasal) the bite-plate was filled with dental putty, which was then placed in the maxillary arcade to create a permanent dental template. This allowed the array to be removed and replaced at a later date with high accuracy. Diagnostic imaging, target identification and planning could therefore be performed ahead of treatment at a later date.
- Acrylic pins; for tumours of the appendicular skeleton, plus soft tissue structures of the pelvis (urethra/prostate), pins were drilled into a reference bone and the bite-plate attached to them with casting material. This was modeled on the stereotactic frame of human SRS and necessitates diagnostic imaging, planning, and treatment under a single anaesthesia.

Given the availability of the Linac to veterinary patients, and the restricted availability of the medical physics support (who ordinarily treated human patients), treatments were single-fractions, typically ranging from 12.5-30Gy depending on the target tumour.

Veterinary Radiosurgery (SRS, SBRS, SRT, SBRT) at the UF-CVM (from 2011)

In early 2011 UF-CVM Small Animal Hospital installed a 21EX Varian Linac with OBI, 120-leaf micro-MLC, optical guidance, and RPM for respiratory gating. The increased availability allowed for the full range of S(B)RS and S(B)RT. Additionally medical physics support was maintained with MBI, plus a full-time radiotherapy technologist (radiotherapist) added.

Tumours treated at MBI/UF-CVM

Brain – Prior to 2000, a stereotactic frame attached to the dog’s skull at the MBI was used. This evolved to using the more convenient dental bite-plate/array construct which can be removed and replaced as necessary. The tumour is imaged with MRI and then a CT performed with bite-plate in the mouth. Both sets of images are fused and used to plan therapy. The commonest tumour treated is meningioma although pituitary masses have also been treated. Close proximity of the mass to the optic chiasm is managed by SRT hypofractionation, typically three doses 48 hours apart. SRT has also been used to treat trigeminal tumours.

Nasal – These have been consistently treated in a single fraction with dental bite-plate both at MBI and UF-CVM. Initially dosing at 12.5Gy, this has been increasing over time to 24Gy for carcinomas and even up to 30Gy for nasal osteosarcoma. Recent data is available for nasal tumours (ECVIM) and will be presented. Despite now treating at UF-CVM, we continue to use cone plans in the nasal chamber rather than the MLC as we have found the sphere-packing plan to conform better to the irregular target. Increasingly nasal tumours are re-imaged at 3-4 months post therapy and residual nasal tumour (if identifiable) removed through rhinotomy.

Limb – SRS of appendicular sarcoma is a common limb-sparing procedure with cases dating back over 10 years (JAVMA 2004). Early patients had large degrees of cortical destruction, but a 30% fracture rate has meant a recent move towards treating earlier lesions with better cortical bone quality. Recent work (VCS) looking at repair of distal radial fractures following SRS is
available. The majority of patients are still treated with a single fraction of 30Gy to the 80% isodose line with optical guidance following the fiducial array attached to the affected bone with pins, although sphere-packing has been replaced by MLC conformal plans. Very occasionally OBI is used for positioning and alignment without an array, but the increased accuracy of fiducial arrays (<0.2mm) over OBI is often necessary with large or distal tumours with little distance between the capsule and the skin.

Urethra (female) – When treated at the MBI, the fiducial array was attached to the wings of the ilium and the urethra covered by longitudinal conformal sphere-packing and ten dogs were treated this way (VCS). Now being treated at UF-CVM, the MLC shortens treatment time although the diagnostic CT and treatment are still performed in a single setting. For the past 2-3 years, these patients have had a cystopexy performed 3-7 days prior to therapy (along with staging lymphadenectomy) to decrease target motion and decrease the risk of a geographical miss. The OBI is used as well as the optical guidance to help refine the technique further. The dose has been typically 25Gy to the 50-60% isodose line, although dose is now more homogenous as the MLC is used over the cones. Increasingly the bladder trigone is being included in the SRS plan, with or without ureteric translocation.

Prostate – Early cases at the MBI relied on pelvic fiducial arrays but the close proximity of the rectum to the prostate limited the deliverable dose to a single fraction and an overly-conservative dose. Now at the UF-CVM, recent cases have been treated with hypofractionated SBRT with doses 48 hours apart, typically 8Gy x 3 fractions.

Heart-base – the problem of respiratory movement was minimized in our patients by respiratory dampening, ie respiratory paralysis and ventilation during natural breaks within the SBRT treatment protocol. Respiratory gating software is available but the simplicity and success of paralysis was encouraging for the future.

Miscellaneous – SRT has been used to treat a cat with nasopharyngeal carcinoma, and several skull base sarcomas and MLO in dogs. All cases used the dental bite-plate fiducial array for lesion localization.

Exotics – no exotics were treated at MBI due to the constraints of requiring optical localization and fiducial markers. With OBI at UF-CVM, more options are available and a rabbit thymoma and King snake skull fibrosarcoma have both been successfully treated using the cone-beam CT and SBRT.

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