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Invited articles

Head frames to image guidance, a brief history of stereotactic radiosurgery

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This concise history of radiosurgery commences with the work of Lars Leksell and the origins of the Gamma Knife which uses ^{60}Cobalt sources. We then continue with the first report of linear accelerator based cranial stereotactic radiosurgery. This is followed by the indications for cranial stereotactic radiosurgery. The evolution of the technique is discussed, including target geometry, isodose shaping, the use of multileaf collimators, dynamic field shaping, scanning beam techniques, CyberKnife robotics, image fusion and treatment optimisation and inverse planning. Finally we consider dose fractionation and extracranial stereotactic radiosurgery (fiducials and respiratory movement).

Key words: radiosurgery, stereotaxis, CyberKnife, image guidance

Early developments

Radiosurgery in its early development was considered to be a surgical technique for treating a sharply defined lesion in the brain by focusing a high single dose of radiation from external sources onto the target lesion. A narrow radiation beam became in effect a new surgical tool but unlike 'real surgery' was a non-invasive technique. The Gamma Unit (it was only later called the Gamma Knife) was developed by the pioneer Swedish neurosurgeon Lars Leksell with the aim of avoiding the necessity of trephining the skull and the consequent risk of infection or intracranial bleeding. In Leksell's own words [1] when he lectured on deep brain surgery at the 50th anniversary meeting of the Harvey Cushing Society in 1981.

> 'Surgery is a conservative art. The skull has been
> trephined since the Stone Age
> and many of our neurosurgical instruments are almost
> as ancient. Modern brain surgery
> became possible when new and fresh tools were
> provided. New developments in physics
> and engineering may allow more radical changes in the
> old surgical handicraft'.

Radiosurgery was initially employed in the field of functional neurosurgery for the treatment of pain, psychosis and movement disorders. In following years its use was extended to the treatment of diseases such as arteriovenous malformations (AVMs) and intracranial tumours. This led to a change of the original definition of radiosurgery and cranial radiosurgery is now considered to be an irradiation procedure for producing a required radiobiological effect (vessel obliteration, tumour control) by focusing radiation from external sources into a stereotactically defined cerebral lesion. Hence the term stereotactic radiosurgery (SRS). In SRS the aim is to deliver a dose to the treatment volume in order to produce necrosis. Two main requirements are essential. Firstly, the precise spatial definition of the target and secondly, a steep fall-off of the absorbed dose at the edges of the target volume.

SRS and its possible general applications were first described in 1949 by Lars Leksell [2, 3] who used a stereotactic frame and moved a 280 kV X-ray source along an arc. The target was precisely located at the geometrical centre of the arc. At this focal point the radiation dose was accumulated by so-called geometrical focusing. This first apparatus was employed for precise irradiation of the gasserian ganglion in cases of trigeminal neuralgia. However, owing to the high scatter fraction of the low energy X-rays, the procedure would have been better performed using high energy particles.

SRS using protons

In 1958-1960 in a series of animal experiments, Börje Larson et al [5, 6] studied the effect of 185 MeV protons on cerebral tissue. This method was applied on a selected number of patients in which a small, well demarcated lesion was obtained in the thalamic nuclei for treatment of movement disorders and intractable pain [7, 8]. Meanwhile other investigators used the end range of the proton or helium ion beam, the Bragg peak. In this region of the beam, the ionising effect is several (usually 4-5)

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times greater than elsewhere; a great sparing effect can be obtained: physical focusing.

Unfortunately, the area of the edge of the beam is narrow where energy delivery is highest and clinical use requires a spread of the ionisation obtained by the use of variable absorbers. However, this artifice reduces the gain between the region of Bragg peak and the rest of the intracranial beam path. Crossfire of 4-12 beams into the target was normally required to achieve an adequate dose fall-off outside the target.

In 1959, Raymond Kjellberg [9] initiated a study using Bragg peak proton beam irradiation at the Harvard 186 MeV cyclotron unit. The pituitary gland was selected first as a suitable target. However, no matter how successful, heavy ion irradiation proved to be cumbersome, from both technical and logistic reasons. The latter were particularly difficult for the Swedish patients, who after stereotactic study performed in Stockholm, had to be transported (whilst wearing the stereotactic frame) to Uppsala for irradiation. This was a 150 km journey.

SRS using ^{60}Cobalt gamma rays

Trying to overcome the problems encountered with proton SRS, Lars Leksell and his colleagues developed in 1967 the first stereotactic irradiation apparatus specifically designed to perform SRS treatment of intracranial targets [10]. This was the Gamma Unit I. In this device an array of ^{60}Cobalt sources, distributed over a spherical sector of 70° x 160° allowed simultaneous crossfire with 170 separated beams with both high mechanical precision and physical reproducibility [11].

This Gamma Unit I was initially used mainly to treat pain. Due to the knowledge gained with gamma thalamotomy [12] the first studies were made of radiobiological problems of large doses delivered in a single SRS treatment session. Nowadays there is no doubt that SRS finds its major application in the treatment of intracranial tumours and vascular malformations, for which the Gamma Unit I proved to be inadequate. In 1975 the Gamma Unit II was introduced [11] with increased diameter circular collimators of 8 mm and 14 mm in order to permit irradiation of larger targets.

By the 1970s Lars Leksell and his colleagues had demonstrated the efficacy of the Gamma Unit II (Figure 1) for the treatment of solid craniopharyngiomas [13], pinealomas, pituitary adenomas [14] and acoustic neuromas [15]. Also Ladislau Steiner et al [16] had performed the first successful obliteration of an inoperable cerebral AVM. Then in July 1979, during a meeting in Paris on stereotactic cerebral SRS, the Swedish school, led by Lars Leksell, and the American school represented by Raymond Kjellberg, presented such an impressive collection of clinical results that seemed to leave very few in doubt concerning the important role that SRS would occupy in the future.

During this pioneering era, SRS was restricted to only a few centres employing various dedicated apparatus such as a Gamma Unit or a cyclotron. Nevertheless, experience was accumulated and the number of candidates for SRS steadily increased. However, although many neurosurgeons had the technical expertise and theoretical knowledge to use SRS procedures, few of them had the possibility to overcome the financial

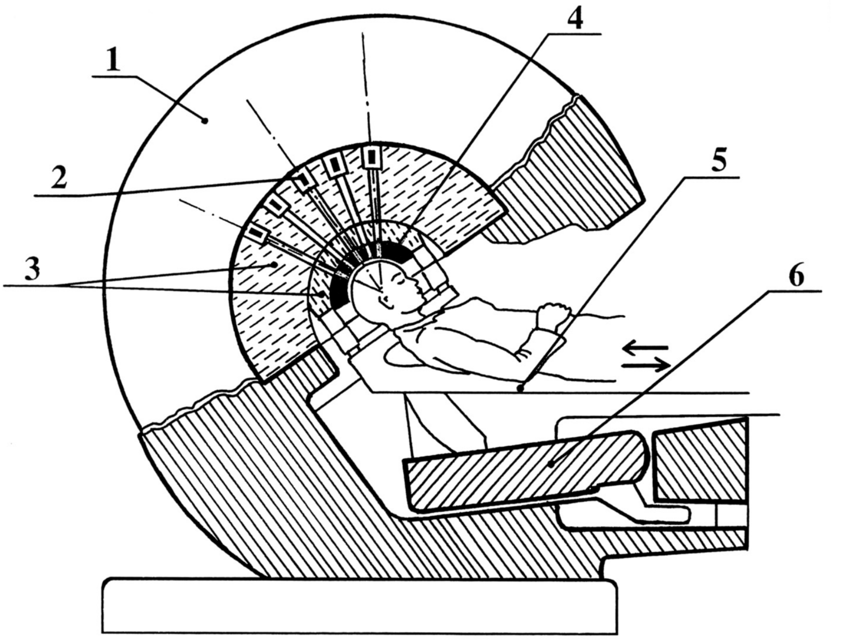

Figure 1. Sketch of the prototype for the Leksell Gamma Knife. (1) Protective housing. (2) In all, 279 ^{60}Cobalt sources 1 mm diameter, distributed over a spherical sector. (3) Primary collimators. (4) Secondary collimators (exchangeable) mounted on the treatment table. (5) Sliding treatment table with stereotactic adjustment of patient position. (6) Folding protection barrier.
Courtesy Professor Rune Walstam [46]

problems related to the acquisition of a Gamma Unit or cyclotron. Barcia Salorio [17] was the first to try to bypass these financial problem by using a standard ^{60}Cobalt teletherapy unit under stereotactic conditions in order to irradiate acoustic tumors and carotid cavernous fistulae.

SRS using X-rays from linear accelerators

In a 1971 monograph, Lars Leksell [10] considered the possibility of employing a linear accelerator but concluded that the final choice of gamma rays rather than high energy X-rays from linear accelerators was determined on technical grounds and on the need for a practical and reliable clinical method. Notwithstanding this authoritative warning, the advent of linear accelerator based SRS was imminent and the first report of a linear accelerator based SRS technique was published in 1983 by Betti & Derechinsky [18]. In its early version the procedure employed a number of isocentric fixed radiation fields in different planes obtained by the rotation of patient's head around a transverse axis.

In 1985 Federico Colombo et al [19] published our technique which was based on multiple converging arc irradiations (Figure 2). A similar technique was reported independently by Gunther Hartmann et al [20]. In the Colombo et al method [19] as in most linear accelerator based SRS techniques, the dose delivery inside the target volume is obtained by using multiple, non-coplanar, arc irradiations. The stereotactically defined target is made to coincide with the linear accelerator isocentre and a single arc irradiation is performed. The target is then rotated around a vertical axis which passes through the isocentre and arc irradiations are repeated in different angular positions which are distributed using a dihedral angle.

Recent interest in linear accelerator based SRS has provided an impetus for neurosurgeons, radiation oncologists and medical physicists to become more involved in this treatment technique. Starting from the basic idea of rotational radiation therapy using moving beam techniques, a variety of ideas have been proposed and tested in clinical practice [21-24] and currently there are more than 1,000 centres utilising a linear accelerator for SRS.

Indications for cranial SRS

In its original version SRS was intended as a means of obtaining the destruction of small volume of precisely located nervous tissue for the purpose of functional neurosurgical treatment. In the early years, the indications for SRS were only for those diseases which could be cured by selective destruction of deep nervous structures [12, 24]. Functional SRS now enjoys a renaissance which we believe has raised more enthusiasm than the results justify [26-28].

Currently SRS finds its main application in the treatment of organic diseases. The indications vary according to the physical and pathological data. Because of the steep dose fall-off which is achieved using SRS, theoretically every lesion with clear-cut borders can be selectively destroyed by an adequate radiation dose. For this reason, benign tumours with non-infiltrating margins [14, 15, 29-31] are thought to be better indications for SRS than are infiltrating malignant lesions [32-34]. The tolerance of neural tissue to single dose SRS definitely depends on the target volume. The opinion that SRS, at least when large single-shot doses are delivered, should be restricted to volumes smaller than 10-15 cm^3 has gained some acceptance. SRS can also be more easily applied to lesions with spherical geometry.

When Lars Leksell introduced radiosurgery, the idea was to avoid the risks of craniotomy and from its inception SRS found general acceptance when prescribed

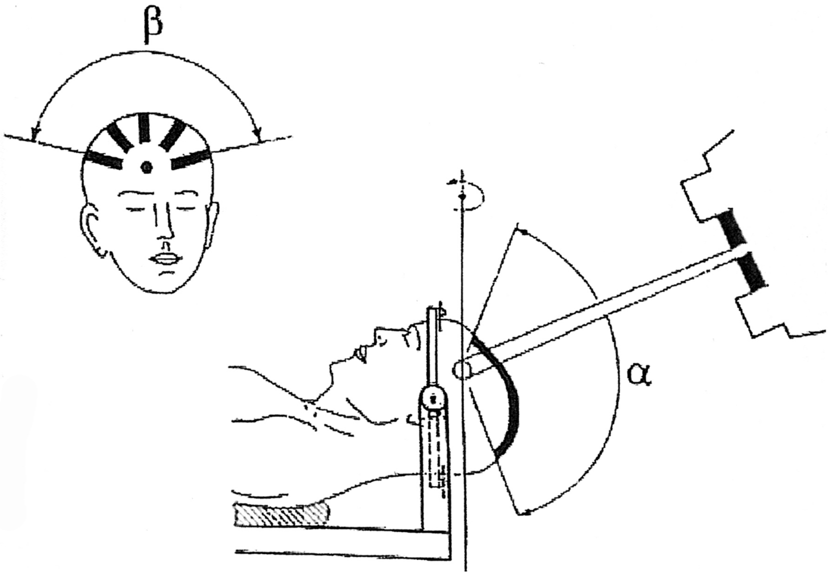

Figure 2. A schematic diagram of the linear accelerator based SRS system used in San Bortolo Hospital, Vicenza since 1982

for treating lesions in which standard craniotomy removal was considered to be either dangerous or impossible. Nowadays the indication for SRS is strongly influenced by the results of microsurgery.

Indications for different SRS techniques can sometimes be due to vague and not generally accepted views. Thus for example, the Gamma Knife is considered by some to be mechanically more accurate and more appropriate to treat lesions very close to critical areas, such as pituitary adenomas. Whereas the linear accelerator is considered by some to permit the treatment of larger volumes of tissue and can if required be employed using multiple fractions. Consequently the linear accelerator is considered by some to provide a better indication for gliomas and other malignant tumours. However, views change as technology evolves.

Evolution of the technique of cranial SRS

In its standard configuration, linear accelerator SRS using fixed circular collimators is well suited for treatment of spherical targets. In clinical practice, however, a perfect spherical shape is more often the exception than the rule and the target volume is often a 3D irregular shape. To try to adapt a spherical isodose to a non-spherical target means either choosing a radiation field which is too large (i.e., giving an overdose to some normal tissues) or choosing a radiation field which is too small (i.e., giving an underdose to some tumour tissue).

Early efforts to treat non-spherical targets employed multiple isocentres to try to conform the dose distribution to the geometrical shape of the tumour/target volume. This technique reduces the irradiation of normal tissue but creates large regions of dose inhomogeneity and may increase the risk of neurological complications. The first attempt to solve this problem was to change the shape of the isodose surfaces by changing the angular approach and the weighting of arc irradiations. Some 3D treatment planning software enables the simulation of different irradiation alternatives by modifying previously defined values for treatment parameters. It is then possible to shape the isodose distributions in predetermined directions so that they conform better to the treatment volume. Isodose curve manipulation is easier to achieve for lower isodoses of less than 50%. Consequently it has been employed more frequently to increase the steepness of the dose gradient adjacent to critical structures such as optical anatomy and the brain stem.

In shaping isodose curves it is generally the case that an increase in isodose gradient steepness in one direction is accompanied by a decrease of gradient steepness in another direction. The use of multiple fixed fields instead of an arc (e.g., six fixed fields for each arc) permits the field to be shaped according to the cross-section of the lesion without increasing the risk of complications. The contour of the lesion according to the beam's eye view can be directly extrapolated by using the treatment planning system. Such a contour can be utilised with a multileaf collimator system for obtaining a required beam shape.

A more up-to-date procedure is dynamic field shaping. In this case the beam is made to conform to the projected shape during each increment of the arc irradiation. This solution requires a computer-driven collimator that during rotation can accommodate the contour of the beam according to the continually changing cross-section of the irregular target volume. In this case however, the mechanical complexity necessary to continuously trim the field for each increment of the arc, limits the possibility of very close correspondence between the beam shape and target contour. Nevertheless a 25% sparing of normal tissue has been reported.

Several techniques have been applied to provide an improvement to the basic converging fields or converging arc planning procedures. However certain isodose shape modifications can be obtained more easily by considering beam geometries which are different from arcs. The real breakthrough for the treatment of 3D irregular targets was to abandon isocentric treatments and to move to scanning beam techniques. This is achieved either (option 1) by applying special devices to existing linear accelerators or (option 2) by moving to completely different robotic apparatus [35]. In option 1 the irradiation is performed by a rectilinear translation of a narrow beam, devised to scan the treatment volume slice by slice. For each slice the target is rotated with respect to the source and the irradiation repeated from different angular positions. A dose is delivered which is proportional to the thickness of the target volume along the beam axis. This is achieved either by modifying the speed of the translation or by inserting a computerised variable absorber. The advantage of the experimental set-up is that it can be applied to every existing linear accelerator. It consists of a motorised treatment couch designed to move the patient along a predetermined direction at a predetermined speed. In order to modulate the dose, couch movement control can be simplified by employing a variable absorber instead of the variable speed of couch translation [35].

Option 2 is to become free from the mechanical restriction of gantry-based systems by introducing robotics and a lightweight narrow beam X-band linear accelerator [36]. In this CyberKnife system the linear accelerator always aims towards the target as it moves along different trajectories around the patient via a computer-driven robotic arm with six degrees of freedom. Standard isocentric or non-isocentric beam techniques can be accurately simulated using a 3D treatment planning system, be thoroughly evaluated and when selected as the most appropriate be accurately reproduced for treatment. Moreover there is no need for a stereotactic head frame. Two orthogonal X-ray assemblies are arranged to define the position of the patient's head in the robot reference system by identifying the bony profiles and comparing them with digitally reconstructed images (DDRs) from CT data. Once the position of the head is determined, the target is reconstructed from recorded computerised examinations and its coordinates transmitted to the robot movement control for aiming the beam. A similar procedure of image guidance is employed in more conventional linear accelerator based SRS systems [37].

Imaging advances represent an important contribution to targeting accuracy in SRS and expand the possibilities for SRS. The very first stereotactic apparatus relied on X-ray projections for aiming at the target. CT was only introduced later. It is important to note that there are two reasons why CT data are essential for SRS. Firstly, dose calculation algorithms rely on information which can be found in CT datasets: namely relative electron density of the medium. Secondly, CT is the tomographic modality which offers the best spatial accuracy: freedom from geometrical distortion as compared to MRI. With its DRR method, the CyberKnife system combines X-ray projections and CT for target localisation. Nevertheless, other imaging modalities than CT have become important for diagnostic purposes and inevitably a need has arisen for the new datasets to be incorporated into SRS planning systems. This integration is made possible by image registration techniques, often referred to as image fusion. MR is the most frequently fused modality to CT. Even though the first applications allowed only rigid movements to be performed, new algorithms for image registration can offer different types of deformation that at least in principle, could account for image distortion. Recent applications open the way to images which are unusual in SRS: PET, rotational angiography and functional MRI [38, 39].

Treatment planning systems evolved from the point of view of treatment optimisation. As techniques become increasingly sophisticated, we need computer programmes to fully exploit conformation capabilities: similar to software used in intensity modulated radiation therapy. The choice of the number and position of beams, is still performed by the operator in many SRS techniques. However, this is now giving way to inverse planning techniques in which the operator makes decisions on prescription and constraints, and the system itself explores the set of possible solutions to find the optimised set-up. The CyberKnife system, by exploiting this type of optimisation strategy and by image guidance with the use of a robotic arm has introduced two important features of great clinical impact: dose fractionation and extracranial radiosurgery.

Dose fractionation

Originally the aim of SRS in the field of functional neurosurgery was to achieve necrosis of a small target volume [12]. With this aim, no real advantage was to be found in dose fractionation: a radiation therapy schedule designed to increase tumour control and to decrease the risk of radiation necrosis. This is the reason why, in the early period, SRS was only performed with high single doses. As target volumes changed from neural tissues to AVMs and benign tumours, no benefit was perceived for fractionation. In contrast the benefits of fractionated regimens are well known in general radiotherapy when dealing with highly proliferative tumours. Fractioned SRS seems to be indicated when large target volumes are involved (since fractionation reduces the risk of normal tissue complications) and when tumours with high proliferative rates are targeted [24, 31]. Intracranial SRS hypofractionation with 3-5 fractions has been suggested and employed as a means of treating larger target volumes (40-50 cm^3) than those usually treated by radiosurgery. This is being employed more frequently as a procedure to preserve important functions where the integrity of involved critical structures is of paramount importance. Two examples are hearing in acoustic tumours, and visual acuity in cranial base meningiomas [40, 41].

Extracranial SRS

A frameless SRS technology such as the CyberKnife (Figure 3), allows ablation of targets anywhere within the body. For intracranial targets a comparison between bony profiles from DRRs and intraoperative X-rays is used for stereotactic localisation to accurately position the patient at the isocentre. This is achieved by matching the bony skull based landmarks from CT based DRRs to those captured by the orthogonal pair of digital X-ray images. The patient is automatically repositioned until a perfect match is made. For targets outside the skull there is a need to define an intermediate spatial reference system that is visible in CT and in conventional X-ray images. For this purpose, before CT scanning usually 3-6 radio-opaque markers must be inserted into or close to the tumour. These fiducials are clearly identifiable in both image datasets. They define unequivocally a spatial reference system that can be employed to transform

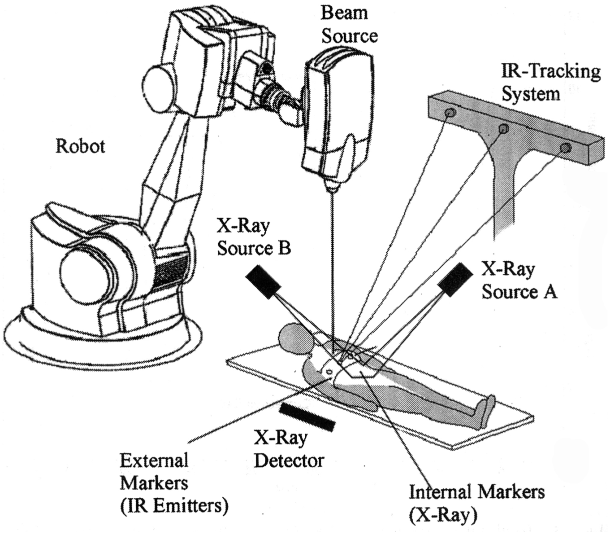

Figure 3. Schematic overview of the Osaka University Medical Center CyberKnife system. Infrared tracking is used to record external motion of the patient's abdominal and chest surface. Stereo X-ray imaging with dual diagnostic energy X-ray sources is used to record the 3D position of internal gold fiducial markers at fixed time intervals during treatment. A robotic arm, with six degrees of freedom moves the 6 MV X-band linear accelerator X-ray beam source to actively compensate for respiratory motion [47]

target coordinates from CT to the robot's reference system [42].

Moreover, since fiducials are inserted into the tumour or fixed to it, image guidance based on radio-opaque markers (fiducial tracking) can also be employed for beam aiming at tumours which move because of respiratory activity in the lung or upper abdomen. In this setting, X-ray imaging is used to accurately track periodic movements connected with respiration and to precisely relate it to the movement of external optical (LED) sources secured to the chest wall. The robot is connected to optical detectors that track the external markers and anticipate the target shift by moving the beam accordingly. The CyberKnife system periodically checks whether the correlation model between internal markers and optical sources is verified. That is, if the target is in the verified position [43, 44].

Conclusions

Image guidance represents a key factor leading to innovation in SRS. Excellent results which parallel those already obtained by frame based SRS techniques have been described for cranial SRS. A main advantage of frameless SRS is the freedom from cranial screw fixation; a procedure which is not easily tolerated by uncooperative patients. Exciting new applications have now become available in spinal SRS in the armamentarium of neurosurgical procedures applicable in both benign lesions (meningiomas, neuromas, AVMs) and malignant lesions (primary and secondary malignant tumours of the spine).

A more problematic use of SRS is in extracranial applications. No matter how precisely focussed the external irradiation by the image guided SRS apparatus, one has to take into account the differences in the biological characteristics of intended targets. For cranial SRS the principal indications are well demarcated lesions. Extracranial SRS has been employed so far for the treatment of large (by cranial standards) malignant tumours of the lung, pancreas, liver, kidney and prostate.

Phase 1 studies have been launched in a restricted number of centres but follow-up is too short for collecting any evidence of efficacy [45]. As neurosurgeons we are now facing a rapid and revolutionary change in a field which we considered to be exclusively our own. We must now be prepared to share our knowledge and our space with other specialties. We hope this will produce major improvements in the treatment of some of the more devastating non-CNS neoplasms.

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