Historical Development of Stereotactic Ablative Radiotherapy

Timothy D. Solberg, Robert L. Siddon, and Brian Kavanagh

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T. D. Solberg (✉)
Department of Radiation Oncology,
Division of Medical Physics and Engineering,
UT Southwestern Medical Center,
Dallas, TX 75390, USA
e-mail: Timothy.Solberg@utsouthwestern.edu

R. L. Siddon
National Naval Medical Center,
Bethesda, MD 20899, USA

B. Kavanagh
Department of Radiation Oncology,
University of Colorado, Aurora, CO 80045, USA

Abstract

Stereotactic radiosurgery (SRS) has been an effective modality for the treatment of benign and malignant cranial disease for over 50 years. Just as SRS revolutionized the practice of neurosurgery, stereotactic ablative radiotherapy (SAbR) in extracranial sites is now challenging conventional wisdom with regard to the practice of radiation oncology. This clinical paradigm change has been enabled in large part through a century of technological development described in this chapter.

1 Introduction

The field of stereotactic ablative radiotherapy (SAbR), beginning with stereotactic radiosurgery (SRS) and later applied to extracranial disease sites (often referred to as stereotactic body radiation therapy—SBRT), has deep roots, with origins in both the surgical and therapeutic radiology disciplines dating back over a century. Since the initial development in 1951, SRS has been well studied through extensive collaboration between

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physicists, radiation oncologists and neurosurgeons. SRS has been refined into an important element in the treatment of brain metastases, cerebral vascular malformations, trigeminal neuralgia and selected primary brain tumors and functional disorders. Modern cranial SRS can be performed noninvasively yet with an extremely high degree of accuracy, and on an outpatient basis. New developments in tumor targeting, image guidance and patient repositioning technology have also allowed for the extension of SRS to lesions outside the central nervous system, including those in close proximity to the spinal cord, where similar concerns about limiting dose to normal tissues apply. Image guidance now plays a particularly important role in the application of SAbR. As a result, recent clinical results in sites including lung, liver and spine suggest an accelerating paradigm shift to high dose-per-fraction delivery in the field of radiation oncology.

2 Early Radiotherapy Experience

The discovery of the ionizing radiation, first observed emanating from a cathode ray tube by Wilhelm Roentgen in late 1895, is well known. It is relevant to note, however, that while this provided the first conclusive evidence of "X-rays," it was almost certainly not the first time they were actually produced, as researchers including Plucker, Crookes and Lenard had experimented with cathode tubes as early as the mid-1800s. Motivated in large part the observation that these invisible "X-rays" were related to fluorescence, Henri Becquerel, followed Roentgen's work with the subsequent discovery of naturally occurring radioactive materials in January 1896. Roentgen would be recognized with the very first Nobel Prize in physics in 1901, and Becquerel similarly recognized (with Marie and Pierre Curie) in 1903.

The significance of these revolutionary breakthroughs was immediately apparent. It is now widely accepted that the first therapeutic X-ray application occurred on 29 January 1986, within weeks of Roentgen's announcement (Grubbé 1933). Interestingly, it is likely that these first therapeutic applications actually predated those used for diagnostic purposes. The first diagnostic application likely occurred on 29 February 1896, when in preparation for a surgical procedure, physicians attempted to image the head of a child suffering from an accidental gun shot (Daniel 1896). The imaging procedure was not successful, though it is relevant to note that three weeks later the child lost all hair in the area corresponding to irradiated region.

The early history of the use of X-rays in therapeutic applications is widely varied and filled with numerous anecdotal accounts. Conditions ranging from eczema, psoriasis, acne, ringworm, portwine stain and hyperthyroidism were common (Tyler 1918). Superficial malignancies were also treated effectively. A major advancement in "therapeutic radiology" occurred with the development of the high vacuum X-ray tube in 1913 by William Coolidge. Within 10 years, and for continuing through several decades, tube potentials in excess of 200 kV would enable therapy of deeper seated tumors. In these early years of radiotherapy, the lack of penetration of low energy X-rays was a well-known shortcoming. To address this, a number of mechanisms were designed to facilitate multi-beam delivery. Notable efforts included the concentric cone approach of Kohl (1906) and Henschke (1938) (Fig. 1a), the pendulum technique of Teschendorf (1953) (Fig. 1b) and the spiral technique of Bischoff (1950, 1952). Bischoff's design was subsequently manufactured and sold by Siemens Reiniger Werke (Erlangen, Germany) (Fig. 1c). Without employing stereotactic localization, these approaches set the foundation for a fundamental radiosurgery principle, namely, dosimetric compactness achieved by targeting with many intersecting, non-overlapping beams.

In the early clinical experience, the prevailing treatment wisdom was that "… therapeutic doses ought to be applied with the highest possible intensity in a short time…" (Matoni 1924). It was also well known, however, that "doses large enough to destroy all of the tumor cells cannot be safely given to adequately large, nonsuperficial areas" (Garland 1934). Through the first three decades of the twentieth century then, the oncologic applications of ionizing radiation were met with limited success. During this era, little was known of the response of cells and tissue as a function of basic radiological characteristics such as time, dose, dose rate. The development of fractionated delivery beginning in the 1920s would change the field in a most profound way. The origins of fractionation are universally attributed to Claudius Régaud, a professor at the Pasteur Institute and director of the radiophysiological laboratory at the Radium Institute (later renamed the Curie Institute after founder and director Marie Curie)

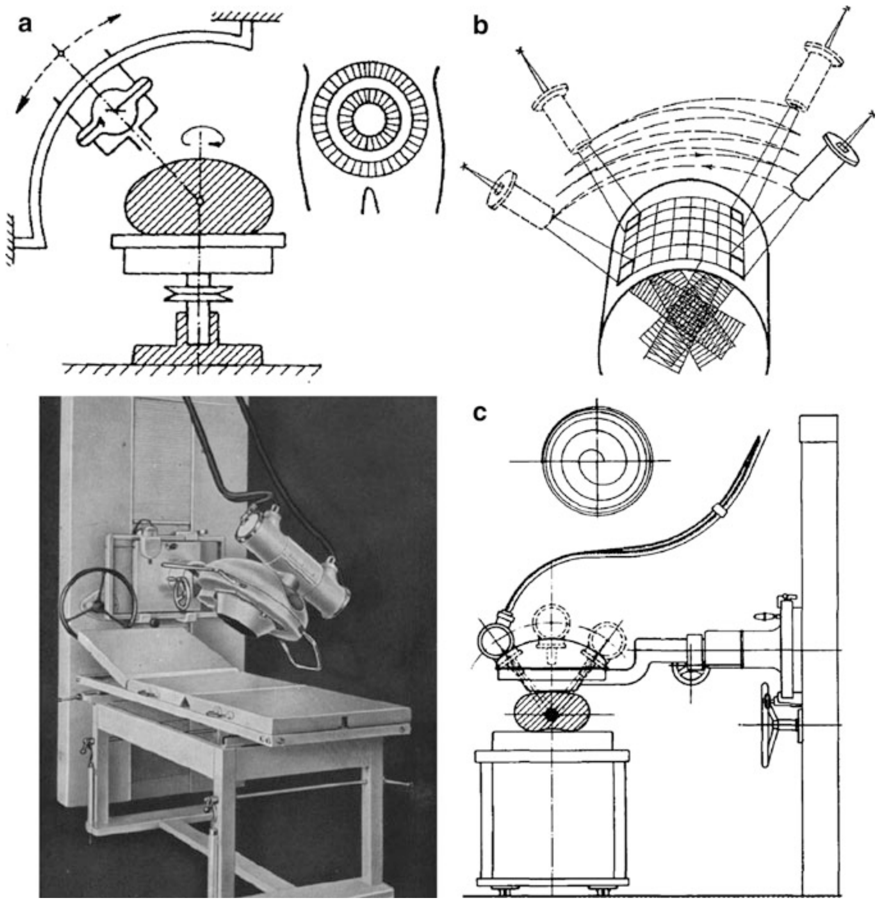

Fig. 1 Early examples of converging beam apparatus designed to compensate for the poor depth dose characteristics inherent in kV X-ray sources. **a** The concentric cone device proposed by Kohl and Henschke; **b** the pendulum approach of Teschendorf; **c** Bischosf's spiral technique, which was subsequently manufactured and sold by Siemens

at the University of Paris. In observing that gross effects were markedly different when radiation was given slowly, such as with radium sources, Régaud began a systematic investigation on the effects of ionizing radiation on spermatogenic cells in rabbit testes (Regaud 1922; Regaud and Ferroux 1927). The resulting observations succinctly stated: "It is impossible to sterilise a rabbit's testicle by a very strong dose of X-rays in a single exposure, without producing a radio-dermatitis. But it is, on the contrary, easy to sterilise this organ, without producing any lesion of the skin, if the same dose is given in five fractions spaced over five to ten days" (Regaud 1929). Régaud extended these observations to clinical practice, with the subsequent observation that "The application of this biological technique has made it possible to obtain much higher percentages of cure, in such cancers as those of the skin, cervix uteri, mouth, pharynx, larynx, antrum of Highmore, etc., whilst preserving the integrity of the normal tissues far more effectually than as formerly possible" (Regaud 1929). The principles of fractionation were subsequently adopted and widely promoted for clinical practice by Henri Coutard (1932, 1937, 1940). To the current day, the clinical practice of radiotherapy owes its existence to the work of pioneers including Régaud and Coutard and others. Yet aside from the possible exception of tumor reoxygenation, fractionated radiation delivery is a suboptimal approach to achieving cure. The ability to safely deliver an ablative dose, demonstrated initially through stereotactic approaches, may significantly improve efficacy of the radiation modality.

3 Origin of Stereotaxis

Stereotaxis is a method for locating points within the brain using an external, three-dimensional (3D) frame of reference, in order to perform a neurological procedure in a minimally invasive manner. The origin

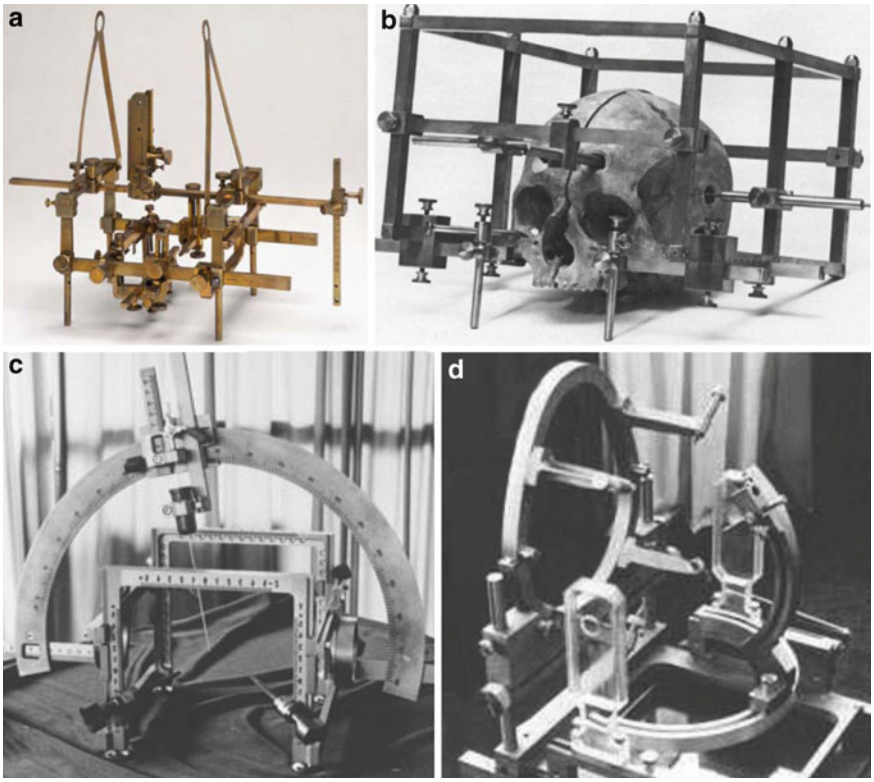

Fig. 2 Early examples of stereotactic frames. **a** The original device of Horsely and Clarke (courtesy of the Science Museum, London); **b** the Mussen frame; **c** an early Leksell frame; **d** an early version of the Todd–Wells frame

and development of stereotaxis, from initial conception and evaluation in animal models to use in humans, share a parallel though independent path with the origin and development of therapeutic radiation. Both date from the early twentieth century, and both saw major progress leading to successful, widespread clinical application beginning at the mid-century mark. The convergence of the two fields at this time is the main subject of this chapter.

3.1 The Stereotactic Method: Horsley and Clarke

It is well known that stereotactic method is the product of Robert Clarke, an engineer, physiologist and surgeon, who, together with neurosurgeon Victor Horsley, devised an instrument for simulating and making lesions at exact locations within the brains of experimental animals. The concept originated with Clarke in 1895, the original device was constructed in 1905 and first used in 1906 (Clarke and Horsley 1906; Fodstad et al. 1991; Jensen et al. 1996). The definitive paper was published in 1908 (Horsley and Clarke 1908), after which the two pioneers ceased further collaboration (Fodstad et al. 1991). Together with other colleagues, Clarke went on to publish functional atlases of both primates and cats (Fodstad et al. 1991). The original device, manufactured by Swift & Son, currently resides in the Science Museum in London (Fig. 2a). Two subsequent copies of Clarke's frame were constructed; one device, brought to the United States by neurosurgeon Ernest Sachs, who had trained under Horsely, is located in the Department of Neurosurgery at UCLA. In the subsequent decades, several efforts were made to improve on the Clarke-Horsley device to make it suitable for human use. The most notable of these efforts was that of Aubrey Mussen (1922) (Fig. 2b), a neuroanatomist/physiologist who worked briefly with Horsley and Clarke. Despite these efforts, there is no evidence that a Clarke-Horsley-type device was ever used on humans. In fact, human stereotaxis would not occur for over 40 years following the landmark work of Clarke and Horsley.

3.2 Clinical Applications of the Stereotactic Method: Spiegel and Wycis

In 1933, Martin Kirschner, a German neurosurgeon, developed a stereotactic apparatus for a skull approach for treatment of trigeminal neuralgia (Kirschner 1933). However, the first successful cranial application of stereotactic surgery in humans is credited to the team of Ernest Speigel and Henry Wycis in the Department of Experimental Neurology at Temple University in Philadelphia (Speigel et al. 1947). Their original frame, using a Cartesian coordinate systems and similar in design and operation to the Clarke-Horsley device, was fixed to a patient's head by means of a plaster cast. The frame and cast were removable, allowing separate imaging and surgery sessions. Contrast radiography, ventriculography and later pneumoencephalography permitted the visualization of intracranial reference points from which the location of target structures of interest could be determined. Initial applications were for psychosurgery, "…in order to reduce the emotional reactivity by a procedure much less drastic than frontal lobotomy" (Speigel et al. 1947). The authors envisioned further application for pain (lesioning of the spinothalamic tract and Gasserian ganglion), movement disorders (pallidotomy), and draining of fluid from cysts (Speigel et al. 1947).

3.3 Widespread Development of Stereotactic Apparatus and Techniques

The work of Speigel and Wycis spawned an enormous interest in the development and application of stereotactic apparatus. The most notable development was the device constructed by Lars Leksell (1949) (Fig. 2c). In contrast to the Cartesian coordinate system of the Speigel-Wycis device, Leksell's frame employed used three polar coordinates (angle, depth and anterior–posterior location). This "arc-quadrant" device provided maximum flexibility in choosing probe entry point and trajectory, and was therefore much easier to use. The frame has been modified over the ensuing years, but remarkably remains very similar in function and appearance to the original 1949 device. Only two years after its development, Leksell would use his frame to target narrow beams of radiation (Leksell 1951). Following the invention of X-ray computerized tomography, Leksell was also quick to build a CT-compatible device (Leksell and Jernberg 1980). Other developments in stereotactic frames included the efforts of Talairach (1949, 1952), Narabayashi (1952), Reichert and Mundinger (1955) and Wells and Todd (1998) (Fig. 2d). The Talairach frame is particularly notable as it was used in the first stereotactic radiosurgery procedure ever performed using a linear accelerator (Betti and Derechinsky 1982). Similarly, modification to the Todd–Wells device resulted in a widely used commercial frame (Brown et al. 1980). The Brown-Roberts-Wells (BRW) coordinate system is the foundation of present day frames made by both Integra Radionics (Burlington, MA) and BrainLAB (Feldkirchen, Germany).

4 The Development of Stereotactic Radiosurgery

By most accounts the concept of using small cross-firing beams of charged particles to ablate or alter the function of cranial structures originated with John Lawrence and Cornelius Tobias in the late 1940s (Tobias et al. 1955; Lawrence et al. 1962; Larsson 1996). Only a few years earlier, the Nobel physics laureate, Robert R. Wilson, had pointed out that protons would have a distinct physical advantage in treating human disease (Wilson 1946). At the time, John's brother Ernest O. Lawrence, Nobel laureate himself for invention of the cyclotron, was director of the Radiation Laboratory in Berkeley, California. John Lawrence was a Harvard Medical School graduate, already known for pioneering work in the field of nuclear medicine which he had been conducting at the Radiation Laboratory since the mid-1930s. Tobias was a graduate student in nuclear physics at the University of California, Berkeley; his Ph.D. committee consisted of Ernest Lawrence, Emilio Segre and Luis Alvarez, all current or future Nobel laureates. Tobias began working with John Lawrence in 1939, prior to receiving his degree; their relationship continued for several decades.

4.1 Lars Leksell and the Early Experience with Stereotactic Radiosurgery

Aware of the work in Berkeley, Lars Leksell, a neurosurgeon working in Sweden, proposed applying the burgeoning methodology of stereotaxis as a means to more accurately guide cross-firing radiation beams (Larsson 1996). In the seminal paper in the field, Leksell coined the term stereotactic radiosurgery, with the radiation beam "…directed to the exact center of the semicircular arch of the stereotactic instrument…." with the target subsequently "…irradiated through a large number of small portals by fixing the semicircular frame at different angles and moving the beam guide transversely along the frame. In this way the whole convexity of the head can be used for the entrance of the beams, which all meet and cross in the structure in question" (Leksell 1951). There are several interesting comments of note in this short, three-page manuscript. First, the word "radiosurgery" appears only in the title of the manuscript, nowhere within the text itself. Second, Leksell admits that ultrasound was investigated prior to applying "Roentgen radiation." Finally, even at the inception, Leksell realized that "radiation of a higher energy" than the 200 kV system presently available was highly desirable.

There is some uncertainty as to when the first clinical radiosurgery application actually occurred. While Leksell's original manuscript includes a picture of a patient in a stereotactic frame, coupled to an X-ray tube, no treatment information is provided. Bjore Larsson recalls the first patient being treated in 1955 (Larsson 1996). In a later manuscript, Leksell described radiosurgery delivered to two patients with tic douloureux treated in 1953 (Leksell 1971). These patients received doses of 1,650 and 2,220 R delivered at 280 kV through 21 and 20 portals with 6 and 10 mm diameter beams, respectively. Both patients had significant, durable relief of their pain.

4.2 Particle Beam Radiosurgery: Uppsala, Berkeley and Cambridge

Larsson and Leksell soon discarded kV X-rays in favor of 185 MeV protons at the Gustaf Werner Institute in Uppsala, Sweden (Larsson et al. 1958, 1963; Leksell et al. 1960). In parallel, the Berkeley group began systematic irradiation of the pituitary gland in patients with advanced cancers, using 340 MeV protons generated by the 184 inch synchrocyclotron at the Radiation Laboratory (Lawrence 1957). Under the guidance of Lawrence and Jacob Fabrikant, the Berkeley radiosurgery program thrived until the early 1990s; the synchrocyclotron was decommissioned in 1987 and the Bevalac in 1993. In 1961, neurosurgeon Raymond Kjellberg began a radiosurgery program using the 165 MeV proton beam facility in Cambridge, Massachusetts (Kjellberg et al. 1968). The Harvard program specialized in arteriovenous malformations and skull base tumors such as chordomas and chondrosarcomas; thousands of patients with these and other histologies were treated before the original cyclotron was decommissioned in 2002. It should be noted that the facilities in Uppsala, Berkeley and Cambridge were never intended for clinical use, but were constructed for physics research. That radiosurgery programs were developed, and many patients successfully treated, is particularly remarkable, and a testament to the efforts of these early pioneers.

4.3 The Advent of the Gamma Knife

Despite significant clinical success throughout the late 1950s and 1960s, particle radiosurgery presented significant shortcomings. Physics research was the main priority at particle facilities, and as a result, access for biological studies and patient treatment was limited. That none of the facilities were hospital-based caused added difficulty for practitioners, as well as anxiety for patients. Motivated by Leksell, the Department of Physical Biology at the Gustaf Werner Institute in Uppsala, headed by Larsson, the Radiation Physics Department physics unit at the University of Lund, headed by Kurt Lidén, and the Department of Clinical Radiation Physics at the National Institute of Radiation Protection in Stockholm, headed by Rune Walstam, began a combined effort to devise a radiosurgery device "suitable for use in a hospital" (Larsson 1996). As a side note of some historic significance, Walstam was also head of Medical Radiation Physics at the Karolinska Institute, a position in which he succeeded Rolf Sievert and was in turn succeeded by Anders Brahme. Earlier, Lidén had presented a preliminary analysis recommending the use of high energy (10–20 MV) Roentgen radiation (X-rays) and suggesting a design with the collimator as close as possible to the patient in order to minimize the geometric penumbra (Lidén 1957; Sarby 1974; Larsson et al. 1974). The result of the collaboration was the "Gamma Knife I," installed at the Hospital

Sofiahemmet in Stockholm in December, 1967. The original device consisted of 179 ^{60}Co sources distributed within at spherical sector of 70° latitude and 160° longitude (Larsson et al. 1974; Larsson 1996). Collimators were designed to provide a beam with a 2.5 × 7.5 mm cross-section with a penumbra width of 0.5 mm at the beam focus (Sarby 1974). Interestingly, much of the original work on collimator design and optimization was performed on a 6 MeV linear accelerator (Varian) (Larsson et al. 1974). In addition to collimator design, Bert Sarby, working at the National Institute of Radiation Protection, also performed the original dosimetry studies (Sarby 1974), and with Hans Dahiln, devised a methodology for calculating the dose distribution resulting from the 179 superimposed beams (Dahlin 1970, 1971; Dahlin and Sarby 1975).

The first two patients were treated in December of 1967 in an experimental hall at the Atomic Energy Corporation in Studsvik, Sweden, prior to moving the unit to the Hospital Sofiahemmet (Larsson 1996). While the device was envisioned and designed for the treatment of functional disorders, early applications also included the treatment of both benign and malignant tumors, as well as vascular malformations (Larsson 1996).

By the mid 1970s, the cobalt sources in Gamma Knife I had decayed significantly. Based on the existing clinical experience, a redesigned device was constructed and installed at the Karolinska Hospital in 1975 (Larsson 1996). This "Gamma Knife II" shared many similarities with subsequent commercial devices, notably, circular as opposed to rectangular collimators. It was even envisioned that the new device might be used for fractionated treatments (stereotactic radiotherapy—SRT) (Leksell et al. 1987; Larsson 1996). Based on the personal relationships between Leksell, Ned Langdon and Robert Rand, professors of radiation oncology and neurosurgery, respectively, at UCLA, the original Gamma Knife was given to UCLA as a gift from the Karolinska Institute and the government of Sweden. Langdon had visited the Karolinska Institute in 1976 and was responsible for securing the necessary approvals to receive the Gamma Knife. Leksell was eager to have the unit used by a major U.S. research center. The unit arrived by ship in San Pedro, California on the morning of July 20, 1980. Later that evening it was loaded on a truck and driven 29 miles to UCLA, under police escort, where it arrived at 2 am on July 21 (UCLA 1980). The unit saw limited clinical and research use before it was returned to Elekta in the early 1990s. Figure 3a shows the original Gamma Knife in use at UCLA.

The first commercial Gamma Knife was installed at the University of Pittsburgh in May, 1987 (Lunsford et al. 1987). Modifications to the original model U Gamma Knife (Fig. 3b) delivered to UPMC, including the models B (Fig. 3c), C and 4C (Fig. 3d), adopted a modified source orientation relative to patient anatomy and allowed for simpler source replacement. In 2007, Elekta released the Perfexion™ gamma unit. The design and operation of the Perfexion are quite different from the Gamma Knife models, with 192 cobalt source arranged in a conical, rather than spherical, configuration (Lindquist and Paddick 2007). Additionally, the 192 sources are divided into eight independent sectors, each of which can dynamically change collimation between 4, 8 and 16 mm circular apertures, as well as a fully blocked position. Through 2008, over 500,000 patients had been treated worldwide on various Gamma Knife models. More detail on design, operation and planning for Gamma Knife can be found in Chapter 2 of this volume.

Another important effort of note was that of the group at the University of Valencia in Spain. Beginning in 1975, Juan Luis Barcia-Salorio, Professor of Neurosurgery, and Gregorio Hernández, Professor of Physics, developed a stereotactic head frame and subsequently, a specialized collimator to a fixed cobalt device which was then rotated around a patient's head; the first treatment was for a carotid cavernous fistula (Barcia-Salorio et al. 1982). Barcia-Salorio was a pioneer in the application of radiosurgery to epilepsy and vascular disease.

Over the years there have been several attempts to replicate the success of the Gamma Knife. The most notable is the Rotating Gamma System designed by OUR New Medical Technology Development in Shenzen, China (Goetsch et al. 1999). The first U.S. installation at the UC Davis Cancer Center in Sacramento, California in 2002 (Kubo and Araki 2002), though few of the units have been delivered outside of China. The successor to OUR, GammaStar Medical Group headed by Shipeng Song, has had tremendous success within China with gamma units designed for both cranial and extracranial radiosurgery. A second

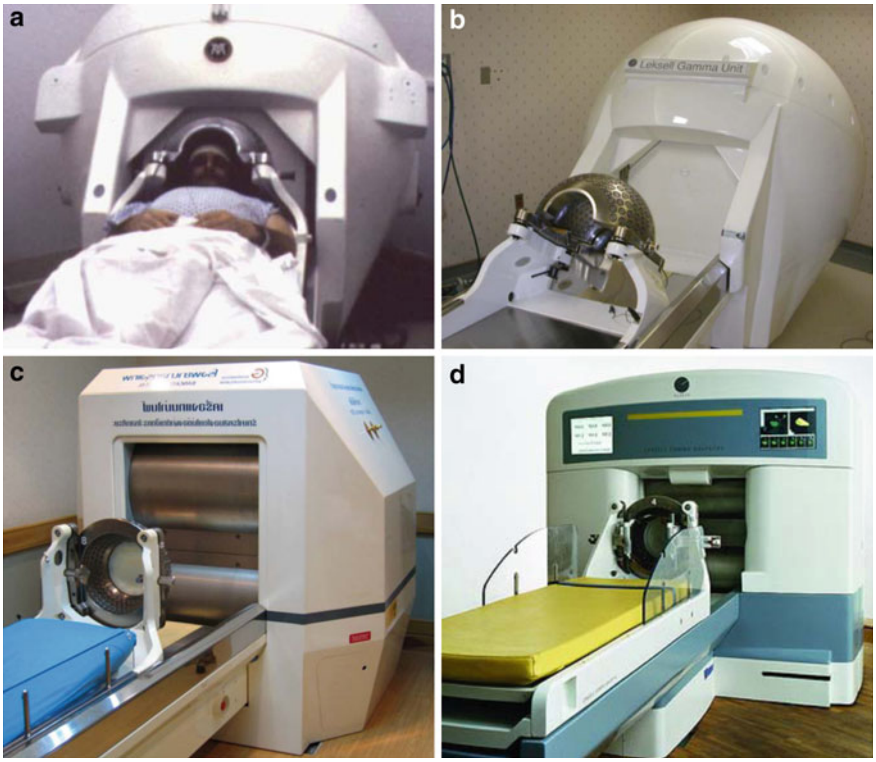

Fig. 3 Evolution of the GammaKnife: **a** the original device, repainted and in use at UCLA Medical Center in the early 1980s; **b** a Model U; **c** a Model B; **d** a Model 4C

Chinese company, MASEP Infini Medical Science Technology Development Co., Ltd. (Shenzhen, China) is developing a next-generation gamma unit similar to the Perfexion^{TM}.

4.4 Linac Radiosurgery

The application of electron linear accelerators to therapeutic radiology was first proposed by Henry Kaplan, chairman of the Department of Radiology at Stanford University, in the late 1940s. Shortly thereafter, Kaplan undertook a collaboration with Edward Ginzton, Stanford Professor of Physics and Electrical engineering, resulting in the development of the first medical linear accelerator, a 4 MeV device that was used to treat a child with retinoblastoma in January, 1956 (Ginzton et al. 1957; Jones et al. 1995). With the subsequent development of isocentric device which could rotate 360°, the first of which was built by Varian and installed at UCLA in 1960, linear accelerators quickly became the essential tool for radiotherapy (Levy 1998). While stereotactic radiosurgery was becoming a routine procedure throughout the 1960s and 1970s, the linacs of that era lacked the accuracy characteristics required for such an application. This was clearly appreciated by Larsson and colleagues as they began the pioneering work which produced the first Gamma Knife: "The choice between the two alternatives, i.e. roentgen or gamma radiation, should be based on technical, clinical and economical rather than physical considerations. If radiation surgery will reach a position as a standard procedure, improved electron accelerators for roentgen production, adapted for the purpose, would seem a most attractive alternative" (Larsson et al. 1974).

4.4.1 Initial Experience with Linac Radiosurgery

Working in Buenos Aires, Argentina, neurosurgeon Osvaldo Betti and Engineer Victor Derechinsky modified a Varian Clinac 18 for use in radiosurgery; the first patient was treated in 1982 (Betti and Derechinsky 1982, 1984). Recognizing that the couch was the weakest mechanical link, Derechinsky designed a specialized chair which supported the patient and to which a Talairach stereotactic frame could be affixed. In the first iteration of the "Betti

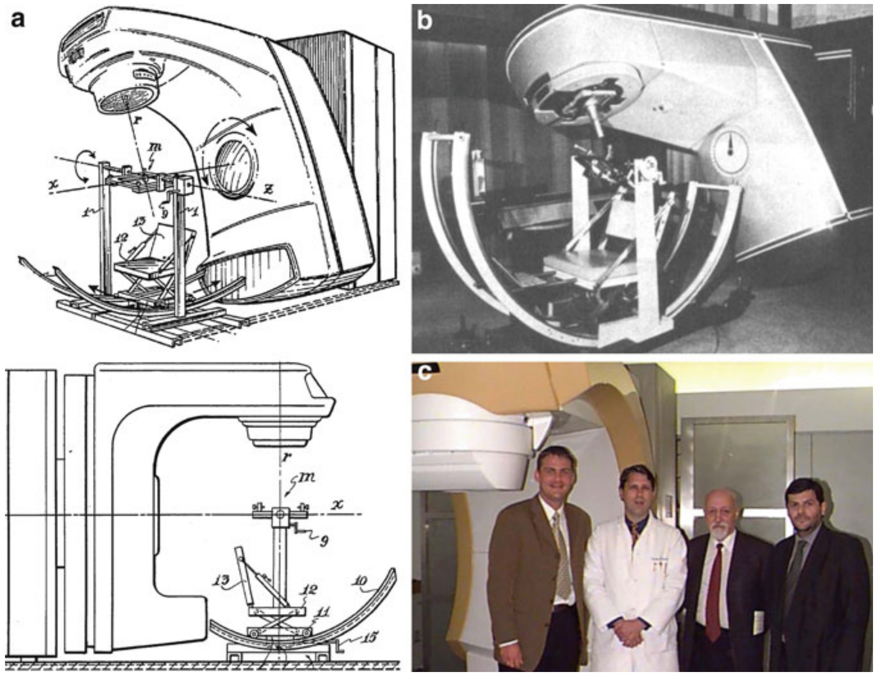

Fig. 4 The original linac radiosurgery system with: **a** drawings from patent awarded to Derechinsky and Betti in 1986; **b** a photograph of the original "Betti chair," installed in Buenos Aires, Argentina; **c** from *left*—Carsten Sommerfeld, Tim Solberg, Osvaldo Betti, and Victor Bourel during a visit to the UCLA Novalis facility in 2000

chair," the patient was physically rotated about a horizontal axis while the gantry rotated about a perpendicular horizontal axis, for providing multiple, convergent beam delivery. The initial chair was subsequently replaced with one that rotated about a vertical axis. In all, three Betti-Derechinsky systems were installed and used, in Paris and Lille, France in addition to the original in Buenos Aires. Interestingly, a copy of the Betti-Derechinsky system was also constructed and used in Bordeaux, France (M. Derechinsky (2010) Personal communication; V. Bourel (2010) personal communication). Illustrations from the patent awarded to Derechinsky and Betti in 1986 are shown in Fig. 4a, with a picture of the original Buenos Aires system in Fig. 4b. Betti and physicist Victor Bourel visited UCLA in 2000 (Fig. 4c) shortly before installing a Novalis unit in Buenos Aires. Shortly after construction of the "Betti chair," a group in Vicenza, Italy, led by neurosurgeon Federico Colombo, developed a stereotactic frame and linac-based SRS system. On an amusing note, the Vicenza group often referred to the Betti chair as a "Cyclothrone."

Linac radiosurgery came to the fore in the late 1980s through the pioneering efforts at four academic centers, located in Heidelberg, Montreal, Boston and Gainesville; Table 1 provides a summary of the early linac SRS practitioners and the techniques employed. Most used specially constructed circular collimators with radiation delivered in one or more arcs at discrete couch positions. The group at the German Cancer Center (DKFZ) in Heidelberg used a commercial Reichert-Mundinger stereotactic frame modified to mount on the couch of a Siemens linac (Hartmann et al. 1985). Concurrently, a large group at the Joint Center for Radiation Therapy and Harvard Medical School on Boston, led by Dr. William Saunders, and later, Dr. Jay Loeffler, was developing a system that would profoundly impact the adoption of linac radiosurgery (Saunders et al. 1988; Loeffler et al. 1989). At the time, mechanical characteristics of the many moving components continued to be the major impediment to a more routine of linacs for radiosurgery. Central among these was the linac couch. To address this, Wendell Lutz constructed a floor stand to immobilize and precisely position a patient's head independent of the radiotherapy couch, without reference to room lasers or light field (Lutz et al. 1984, 1986, 1988). Intrinsic to the system was a patient-specific QA process in which a radio-opaque ball mounted to a BRW ring was attached to the floor stand. After establishing the patient's target coordinates on the floor stand, a series of films at eight representative gantry and couch positions were

Table 1 The initial LINAC radiosurgery experience

Reference	First Tx	Energy (MV)	Patient support	Frame
Betti and Derechinsky (1982, 1984)	1982	10	Institution-designed chair	Talairach
Colombo et al. (1985)	1982	4	Linac couch	Institution-designed
Hartmann et al. (1985)	1985	15	Linac couch	Reichert-Mundinger
Lutz et al. (1984, 1986, 1988)	1986	6	Floor stand	BRW
Podgorsak et al. (1987, 1988)	1986	6 and 10	Linac couch	Institution-designed
Friedman and Bova (1989)	1988	6	Floor stand	BRW

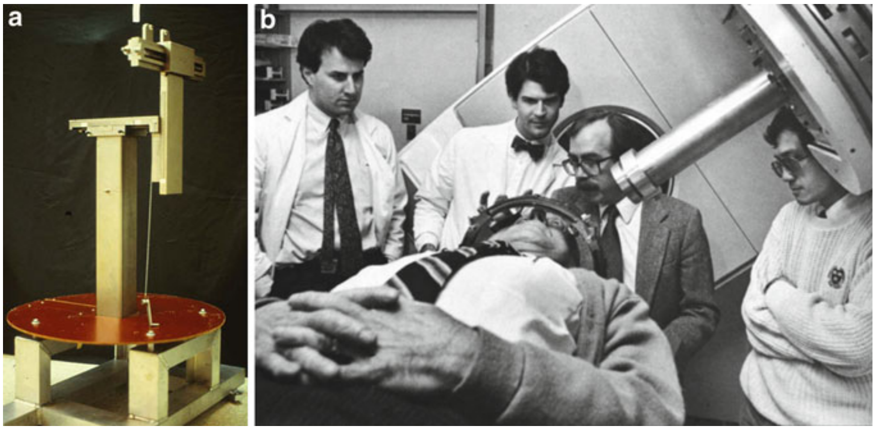

Fig. 5 **a** An original floor stand and irradiation approach from the Brigham and Women's Hospital/Joint Center for Radiation Therapy; **b** a photograph of an early SRS treatment at the Brigham and Women's Hospital. From *left*: Jay Loeffler, Eben Alexander III, Bob Siddon and Chee Wai Cheng

obtained (Saunders et al. 1988; Lutz et al. 1988). In this manner patients could be accurately localized without depending on external marks or room lasers. The procedure of obtaining isocenter ball shots is now universally referred to as the "Winston-Lutz" test, though largely in the context of machine QA, and not patient QA as originally designed. Lutz left for the University of Arizona in 1985, where he continued to manufacture floor stands and collimators which he sold at his cost for approximately $14,000. Floor-stand linac radiosurgery systems became quite common over the subsequent decade. Figure 5a shows example of one of the initial floor stand, with an early patient treatment at the Joint Center in Fig. 5b.

The floor stand development efforts were complemented by those of a number of Harvard scientists in localization, dosimetry and treatment planning. A method for localization of intracranial targets using a pair of radiographs was developed by Bob Siddon and Norman Barth (Siddon and Barth 1987). This method, with submillimeter accuracy, continues to be the gold standard for AVM localization to this day. Much of the initial cone dosimetry was performed by Roger Rice (Rice et al. 1987). Both Barth and Rice were Harvard post-docs at the time. Siddon wrote the original treatment planning system on a Mac II; this was subsequently rewritten on a specialized graphics computer (Kooy et al. 1991). Svensson (1989) and Tsai et al. (1991) made significant contributions to furthering quality assurance efforts. A linac radiosurgery conference held in Boston in 1987 included many notable scientists and clinicians from throughout the world (Fig. 6).

While the floor-stand approach addressed a major source of inaccuracy, namely the linac couch, the gantry rotation characteristics of existing linacs of that time was also quite poor. To address this, a group at the University of Florida in Gainesville, led by Frank Bova and Bill Friedman, followed on the work of the Harvard group, by designing an isocentric arm which coupled the source and collimator, through a high precision bearing, to the floor stand, thereby improving the accuracy associated with gantry rotation (Fig. 7a) (Friedman and Bova 1989). To avoid torque on the linac head, a gimble-type bearing was developed to hold the tertiary circular collimators. These efforts

Fig. 6 An early linac SRS symposium in Boston in 1987. Those in attendance included: Eric Cosman, Ken Winston, Peter Black, Peter Heilbrun, Goran Svennson, Bob Siddon, Dennis Leavitt, Frank Bova, Bill Saunders, John Adler and Rock Mackie

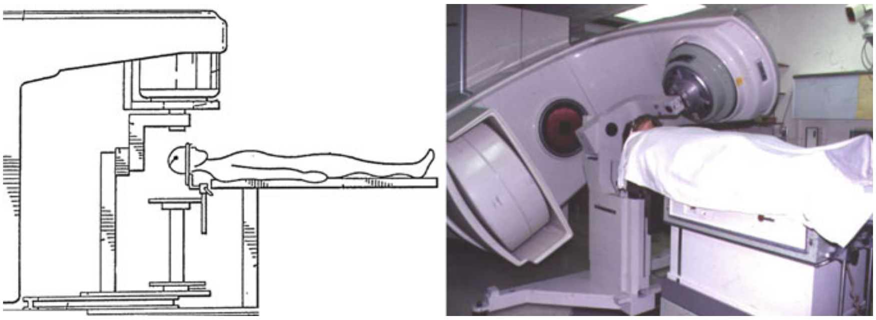

Fig. 7 Drawing from the 1993 patent awarded to Frank Bova and Bill Friedman. The commercial version of the Bova-Friedman design (Philips SRS200) is shown in clinical use at UCLA in 1992

resulted in the first complete, commercial linac radiosurgery system—the SRS 200 (Philips Medical Systems). The SRS 200 system included the Gainesville floor-stand apparatus and CT-based treatment planning system, a BRW stereotactic frame and other components from Radionics, and circular collimators with nominal diameter from 10 to 32 mm in 2 mm increments. In an era when vendors also distributed source code, enhancements to the treatment planning system, including MR imaging and planning capabilities (by the group at Vanderbilt University) were developed by several SRS200 customers. An SRS 200 system was installed on a Clinic-18 at UCLA Medical Center in 1989 (Fig. 7); approximately 450 radiosurgery patients were treated between 1990 and early 1996. Thanks to the work of the Harvard and Gainesville groups, floor-stand linac radiosurgery systems became quite common over the subsequent decade. Gainesville "Linac Scalpel" changed commercial hands several times, from Philips to Medtronic Surgical Navigation Technologies (Minneapolis, MN) to Zmed (Boston, MA), which were subsequently acquired by Varian Medical Systems (Palo Alto, CA) in 2003.

Another significant early contribution occurred at McGill University in Montreal, where a group directed by Luis Souhami and Ervin Podgorsak modified two linacs for radiosurgery. A single plane rotation technique was developed for a 6 MV linac (EMI Medical, Sunnyvale, CA) while a technique employing simultaneous and continuous gantry and treatment couch rotation was developed for a 10 MV linac (Varian Clinac-18). The "dynamic radiosurgery" approach was used for targets in close proximity to important structures and where a sharp dose gradient was required. The group used a frame of their own design (Olivier et al. 1986), mounted to either of the linac couches. A treatment planning system supporting both CT and MR was developed by Pike et al. (1987a, b).

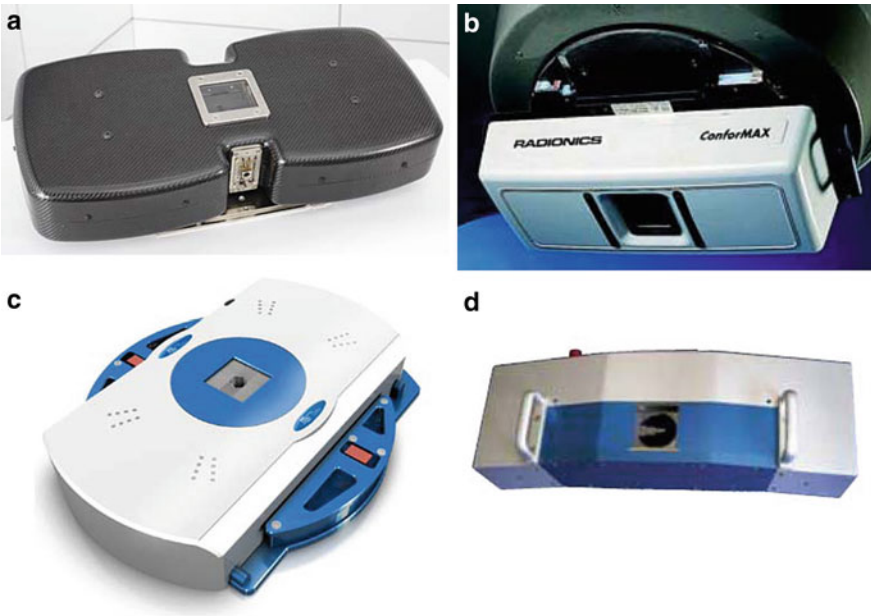

Fig. 8 Micro-Multileaf collimators from **a** MRC systems (later Siemens); **b** Radionics; **c** BrainLAB; **d** 3D Line

4.4.2 The Advent of Micro-Multileaf Collimators

Through the mid-1990s, radiosurgery, whether delivered by cobalt, linac or particle beams, was performed using circular collimators. Because most tumors are not spherical in shape, the use of circular collimators often necessitated a compromise between plan quality, treatment time and dose heterogeneity. Leavitt et al. (1991) were the first to address the issue of field shaping by adding two sets of upstream independent trimmers ("vanes") to the auxiliary circular radiosurgery collimators. The trimmers were motor controlled, and could rotate about the beam axis as well translate in and out. With a single isocenter, the authors demonstrated markedly improved conformality over circular collimation alone. A similar, albeit non-dynamic approach was subsequently developed and implemented by Hacker et al. (1997). This methodology became available commercially in the XKnife planning system (Radionics, Inc., Boston, MA).

Modeling studies by both Leavitt et al. (1991) and Nezdi et al. (1991, 1993) generated increasing interest in more sophisticated field shaping apparatus. As a result, a group at the German Cancer Research Center (DKFZ) in Heidelberg group, who earlier had produced a number of significant developments, developed the first micro-multileaf collimators using for cranial radiosurgery (Schlegel et al. 1992). Two designs with 3 mm wide leaves were constructed, one in which the leaves were positioned manually, and a second with motorized, computer-controlled leaves. Both mounted directly to the auxiliary device holder on most linacs. The ModuLeaf MLC technology was commercialized by a DKFZ spinoff (MRC Systems, Heidelberg, Germany), and was subsequently sold to Siemens Medical Solutions (Malvern, PA) (Fig. 8a).

Shiu et al. (1997) described the development and characteristics of a miniature multileaf collimator designed specifically for small field cranial radiosurgery. The MLC consisted of 15 pairs of leaves projecting a width of 4 mm at isocenter, for a maximum field size of 6×6 cm^2. Treatment planning was facilitated using the XKnife system (Radionics, Burlington, MA). A 27 leaf pair version with a maximum field size of 13.4×10.8 cm^2 was subsequently commercialized by Radionics (Fig. 8b). Concurrently, the m3, a 52 leaf micro-MLC was developed jointly by BrainLAB GmbH (Heimstetten, Germany) and Varian (Fig. 8c). The m3 had 14 pairs of 3 mm leaves located in the center of the field, 6 pairs of 4.5 mm leaves in the middle and 6 pairs of 5.5 mm leaves at the periphery for a maximum field size of 10.2×10.0 cm^2. Physical and dosimetric characteristics of the m3 have been described by Cosgrove et al. (1999) and Xia et al. (1999). In the ensuing years, the Radionics and BrainLAB micro-MLC have been installed on a variety of linacs, and

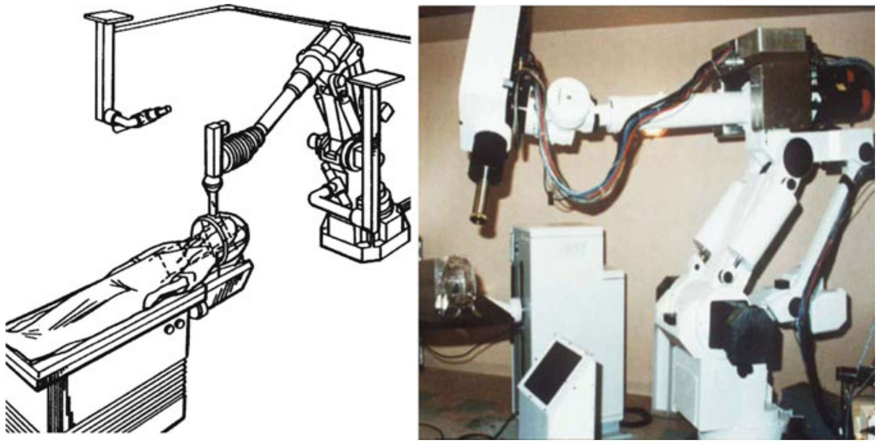

Fig. 9 Drawing from the 1993 patent awarded to John Adler, Russell Schonberg and Peter Schonberg, with an early version of the CyberKnife

continue to be used to this day in the treatment of many patients every year. Meeks et al. (2000) described a double-focused miniature MLC developed in conjunction with Wellhofer Dosimetrie (Schwarzenbruck, Germany).

4.4.3 Dedicated Linac Radiosurgery Systems

Through the 1990s, the use of linacs in radiosurgery remained controversial, based largely on the assertion by some practitioners that linac-based systems, with multiple moving parts, could not match the accuracy of gamma units. While the work of Friedman and Bova rendered this argument largely specious, it remained a common perception. In part to counter this argument, several notable efforts aimed at developing linacs dedicated exclusively to radiosurgery applications were initiated. Their efforts culminated in a robot-mounted linac (CyberKnife, Accuray, Santa Clara, CA), a C-arm multi-rotation-axis linac (Mitsubishi Electric Ltd., Tokyo, Japan), a conventional linac single energy 6 MV photon with a fixed 10 cm diameter primary collimator (600SR, Varian) and a linac with an integrated micro-multileaf collimator (Novalis, BrainLAB). Each of these are described briefly.

4.4.3.1 The CyberKnife

In 1989, John Adler, a neurosurgeon working at Stanford University, conceived the idea of new radiosurgery device consisting of a compact, robot-mounted linac. Adler approached Schonberg Radiation Corporation (Santa Clara, CA) for assistance in building a linac with the necessary requirements (size, weight, energy, dose rate, etc.). SRC was founded by Peter and Russell Schonberg; Russell had previously worked as manager of electrical systems at Varian Associates where he worked on the development of medical linear accelerators. Russell also developed a portable electron linac which eventually became the Mobitron (IntraOp Medical, Santa Clara, CA) (Schonberg 1987). Patent number 5,207,223 was awarded in 1993 to Adler and the Schonberg brothers, and assigned to Accuray. A diagram form the patent award and a photo of the original prototype at Stanford are shown in Fig. 9.

Originally called the Neurotron 1000 (Adler 1993; Cox and Murphy 1995), the first system consisted of a 300 pound, 6 MeV x-band (9.3 GHz) SRC linac, mounted to an industrial robot (GMF, Auburn Hills, MI) (Adler and Cox 1996; Adler et al. 1997). The robotic configuration eliminated the isocentric constraint of radiation delivery. From the time of its inception the system was intended to facilitate frameless radiosurgery, performed using a stereo pair of X-rays (Guthrie and Adler 1991a, b; Adler 1993), and the Accuray founders deserve considerable credit as pioneers in image-guided radiotherapy (IGRT). In 2001 the CyberKnife received FDA approval to treat indications anywhere in the body. Using anthropomorphic phantoms, submillimeter accuracy has been demonstrated in cranial and spinal applications (Chang et al. 2003; Yu et al. 2004). CyberKnife is now a mainstay in both cranial and extracranial stereotactic treatments.

4.4.3.2 The 600SR

To address the burgeoning radiosurgery market, Varian released a linac dedicated to radiosurgery applications in 1994. The first 600SR unit was installed at Brigham and Women's Hospital in Boston; subsequent 600SR installations included: the Thomas Jefferson University in Philadelphia (Andrews et al. 2006), the Rigshospitalet in Copenhagen, Apollo Cancer Institute in Delhi, India, the Klinikum Der Westfalische Wilhelms-Universitat in Munster, Germany and the University of California, Los Angeles. Modeled after the 600C, the 600SR was a single energy 6 MV linac, with a redesigned flattening filter and a fixed primary collimator 10 cm in diameter. The smaller flattening filter resulted in dose rates up to 800 MU/min in clinical mode, and nearly 1,300 MU/min in service mode. Radiation was delivered in the conventional rotational manner, with an MU/degree range from 0.3 to 20.0 to facilitate both high (SRS) and low (SRT) dose-per-fraction delivery. The machine had no movable diaphragms, and the lighter treatment head coupled with reduced counterweight and the new Varian ETR couch resulted in a compound accuracy (gantry, couch and collimator rotations) of <0.9 mm as measured with a Winston-Lutz test (Das et al. 1996). All of the 600SR units were packaged with stereotactic hardware (frames, collimators and QA equipment) and treatment planning systems (XKnife) from Radionics.

4.4.3.3 The Mitsubishi C-arm Linac

In 1996, Mitsubishi Electric Company, Limited (Tokyo, Japan) introduced a unique linac with two rotational axes designed for radiosurgery. The linac head was mounted on a C-arm which rotated 60° about a horizontal axis perpendicular to the gantry rotational axis. The unit operated at 4 or 6 MV, with a variable dose rate to 450 MU/minute, and circular collimators from 0.5 to 3.5 cm in diameter (Tamaki et al. 2000). The linac was also equipped with a 120 leaf MLC, with the central 80 leaves projecting 5 mm and the outer 40 leaves projecting 10 mm at isocenter (Nakagawa et al. 2003). Another unique feature included a small CCD video camera attached to the center of the linac gantry used to determine geometrical accuracy; an isocenter precision of $\pm$ 0.8 mm, including C-arm, gantry and table rotations, was reported, $\pm$ 0.8 mm. (Nakagawa et al. 2003).

4.4.3.4 The Novalis

Shortly after delivering the last 600SR to UCLA, Varian extended their collaboration with BrainLAB with an agreement to integrate the BrainLAB m3 collimator onto the 600SR platform. The result was the Novalis-Shaped Beam Radiosurgery System, the first of which was installed at UCLA in 1997; the first Novalis treatment occurred in early 1998. The succession of Novalis units, from the original UCLA device to the current day Novalis Tx, is shown in Fig. 10. The ability to treat increasingly more complex geometric targets using a single isocenter produced dose distributions that are both more conformal and more homogeneous than traditional techniques (Solberg et al. 2000a, b; Andrews et al. 2006). The development of dynamic arc delivery, in which the leaves move during rotational delivery to continuously shape to the beams-eye-view projection of the target, further improved conformality and reduced average treatment times to approximately 15 min (Solberg et al. 2001). Circular collimators mounted beneath the MLC enabled the Novalis to become the first linac system used routinely in the treatment of trigeminal neuralgia (Solberg et al. 1998; Goss et al. 2003; Smith et al. 2003). In 2000, BrainLAB provided an IMRT solution for the Novalis, with inverse planning based on the dynamically penalized maximum likelihood (DPL) algorithm described by Llacer (1997). Theoretical and practical characteristics of the DPL algorithm, including performance under gated operation, have been described by several authors (Chetty et al. 2000; Arellano et al. 2000; Solberg et al. 2000a, b; Llacer et al. 2001; Hugo et al. 2002; Agazaryan et al. 2003). In 2001 BrainLAB introduced their image guidance system based on stereoscopic X-ray imaging. The first generation utilized two ceiling-mounted diagnostic tubes projecting on a single couch-mounted flat panel detector (Fig. 10b). Later generations were implemented with the two tubes recessed in the floor, projecting on two opposing ceiling-mounted detectors (Fig. 10c). The current BrainLAB/Varian offerings include the Novalis Tx (Fig. 10d) (Chang et al. 2008) and the Novalis powered by TrueBeam STx.

5 The Development of Stereotactic Body Radiation Therapy

The success of cranial SRS as an efficient, potent means of local tumor treatment eventually prompted several groups to evaluate analogous strategies of high dose-per-fraction treatment to extracranial tumors in a variety of sites away from the nervous system. Very much influenced by Leksell's use of a

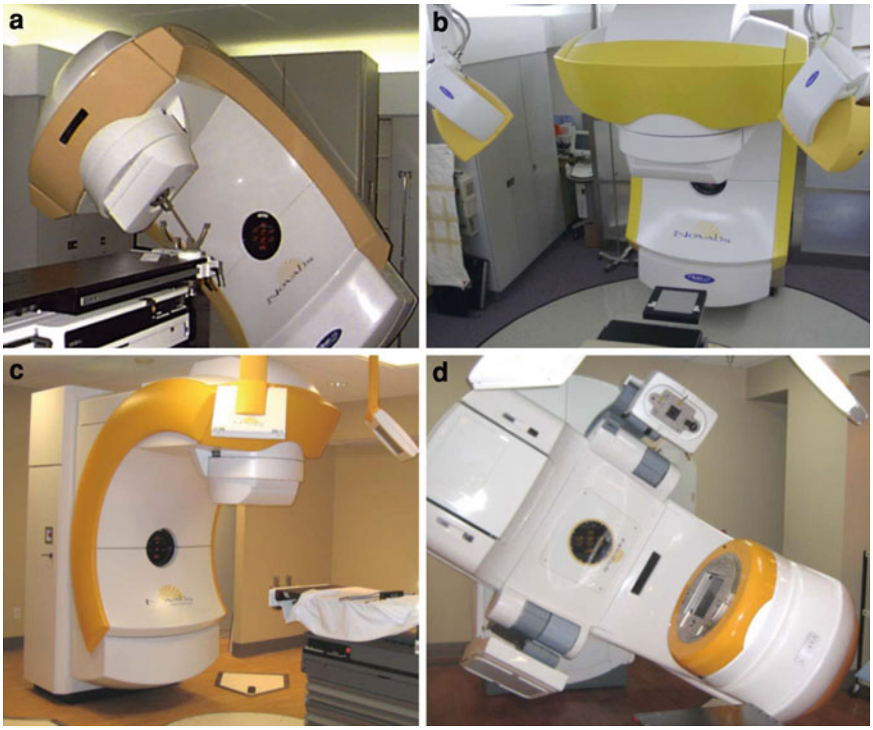

Fig. 10 Evolution of the Novalis: **a** the original device at UCLA in 1997; **b** the UCLA device with original ExacTrac X-ray system in 1999; **c** a Novalis with upgraded ExacTrac X-ray system; **d** the Novalis Tx

rigid frame to stabilize the head during cranial SRS, initial efforts by several groups in Sweden, Arizona, New York, Houston and elsewhere followed a frame/fiducial-based paradigm for localization of extracranial targets. With the advent and now widespread adoption of in-room image guidance, the frame-based approaches have been largely relegated to history. Nevertheless, many patients were successfully treated with doses using frame-based approaches, and the field is indebted to these early pioneers in demonstrating what can be clinically achieved through the accurate administration of ablative dose of radiation. Though the acronym SBRT (stereotactic body radiation therapy) is widely used to describe extracranial application, a more appropriate nomenclature, stereotactic ablative radiotherapy (SAbR), has been proposed by Loo et al. (2011). In this chapter, SBRT and SAbR are used synonymously.

5.1 The Karolinska Experience and the Stereotactic Body Frame

Beginning in 1990, a group from the Karolinska Hospital in Stockholm, Sweden, began development of a methodology for SBRT localization that, due largely its non-invasive nature, found broad clinical acceptance in the intervening years (Lax et al. 1994; Blomgren et al. 1995). The system consisted of an immobilization box with embedded CT fiducials, and a device for compressing the chest to limit respiratory motion (Fig. 11). Localization accuracy was limited to "5–8 mm in 90% of setups," due to large difficulty in reproducing the patient's position within the box between imaging and treatment sessions. A unique feature of the body frame was a mechanism for abdominal compression, which was very effective for limiting motion due to respiration (Negoro et al. 2001). The system was commercialized by Elekta AB (Stockholm, Sweden) as the Stereotactic Body Frame® and used clinically at a number of institutions throughout the world (Wulf et al. 2000; Nagata et al. 2002; McGarry et al. 2005; Hansen et al. 2006). Elekta recently discontinued the Stereotactic Body Frame.

5.2 The Tucson Experience with Spinal Radiosurgery

A methodology for radiosurgery of targets involving and adjacent to the spine was described by Hamilton and Lulu (1995). The system consisted of a shallow

Fig. 11 **a** The Elekta Stereotactic Body Frame, based on the original design of Lax and Blomgren; **b** the abdominal compression feature of the SBF is very effective at reducing motion associated with respiration

rigid box, with lateral dimensions compatible with CT imaging (Fig. 12). Patients were placed within the box in a prone position, and under anesthesia, small clamps were attached to one or two spinous processes adjacent to the intended target. These clamps were rigidly attached to two semicircular metal arches secured to the box. The stereotactic space was defined relative to a small radio-opaque sphere using the coordinate system of the CT scanner. Imaging, planning and treatment were performed in a single setting with the patient rigidly fixed for the duration of the procedure. The authors reported localization uncertainties of 2.0 mm in a worst case scenario. This prototype spinal system was subsequently used in the treatment of nine patients (Hamilton et al. 1995, 1996). Doses delivered were understandably conservative, ranging from 8 to 10 Gy, with distributions constructed in such a way that no portion of the spinal cords received more than 3 Gy. An attempt to commercially market the "Arizona" spinal radiosurgery system proved unsuccessful.

5.3 Other Frame-Based Approaches to SBRT

In the late 1990s the group at the German Cancer Center (DKFZ) in Heidelberg described the development and clinical application of a stereotactic body frame. A metal arch with v-shaped fiducials, rigidly mounted to a full length carbon fiber board, established a CT-based coordinate system in the standard manner (Lohr et al. 1999). Patients were fixed to the frame through the use of a torso-length body cast. Fixation of the patient within the frame can be obtained with a vacuum pillow, or, as presented here, with a Scotchcast body cast. Mean overall accuracy of the system was reported as $\leq$3.6 mm. The authors recommended repeat CT imaging immediately prior to treatment, "…since an acceptable result of repositioning could be achieved in only less than one-half of the patients on the first attempt" (Herfarth et al. 2000). Extracranial targeting accuracy could be improved by supplementing the body cast with a head

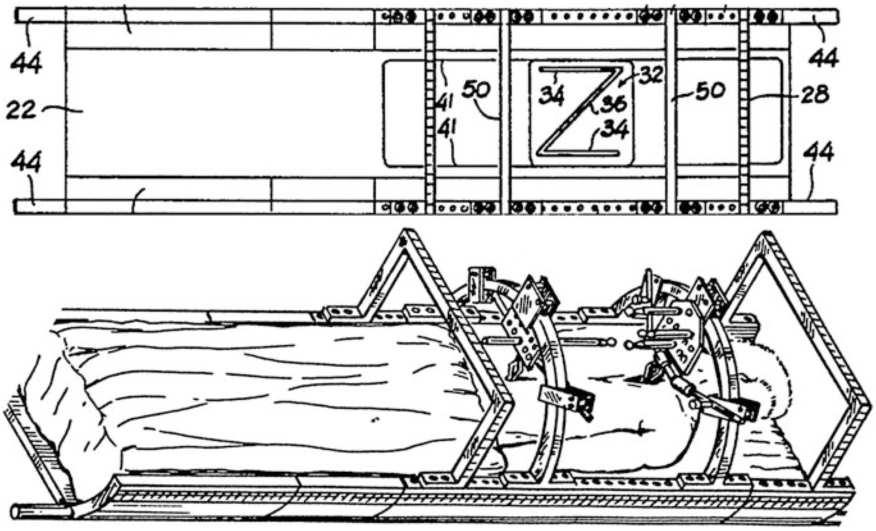

Fig. 12 The Arizona spinal radiosurgery concept, as illustrated in the drawings from the patent awarded to Hamilton and Lulu in 1994, with the common "*Z*" fiducial configuration for tomographic localization

fixation. An abdominal compression device added subsequently proved effective in reducing respiratory motion. The system was commercialized by Leibinger (Freiburg, Germany: Fig. 13b), and went through a series of commercial hands before being discontinued by Stryker (Kalamazoo, MI).

6 SRS and SBRT in the Era of Image Guidance

Targets outside the skull are not readily amenable to fixation using rigid frames, and therefore in present day applications, image guidance is a prerequisite for extracranial SRS and SBRT. As with frame-based radiosurgery, "frameless" technologies were initially developed to facilitate surgical applications. The first reference depicting frameless capabilities was published by Roberts et al. (1986), who described a method for registering CT data with an operating microscope for neurosurgical applications. Subsequent investigators refined this approach (Kato et al. 1991; Guthrie and Adler 1991a, b; Tan et al. 1993), and frameless neuro-navigation is now commonplace.

6.1 Image-Assisted Frame-Based SBRT

Obvious shortcomings in accuracy of frame-based approaches prompted early SBRT-practitioners to develop image-based methods for target verification. Initial approaches certainly incorporated portal imaging.

Yenice et al. (2003) described frame-based SBRT combined with daily CT imaging performed just prior to each treatment. To facilitate improved reproducibility, the patient was setup initially in a standing position, after which the frame and patient were tilted backwards into a horizontal treatment position. The authors were able to demonstrate a localization accuracy of within 1 mm (1σ) in any direction. Daily CT was eventually replaced with localization based on electronic portal imaging, with little loss of targeting accuracy (Lovelock et al. 2005).

Motivated by a desire to treat spinal lesions, the group at UCLA designed and constructed a series of body frames beginning in 1993; an early version, never used clinically, is shown in Fig. 13a. Subsequently, Medin et al. (2002) proposed a minimally invasive localization technology that allowed for high-dose, single fraction irradiation of tumors near the spine. Under local anesthesia, three small radio-opaque markers were permanently affixed within the vertebral and spinous processes. The implanted fiducials were localized on biplanar radiographs obtained at the time of the planning CT. Imaging procedures utilized an external localization box from which a coordinate system was established (Fig. 14). At the time of treatment, biplanar radiographs were repeated in the treatment room using a mobile radiography unit. The implanted fiducials were identified, and the isocenter position was calculated based on the geometric relationship between the target and implanted markers obtained at the time of CT imaging. In this manner, accurate target localization could

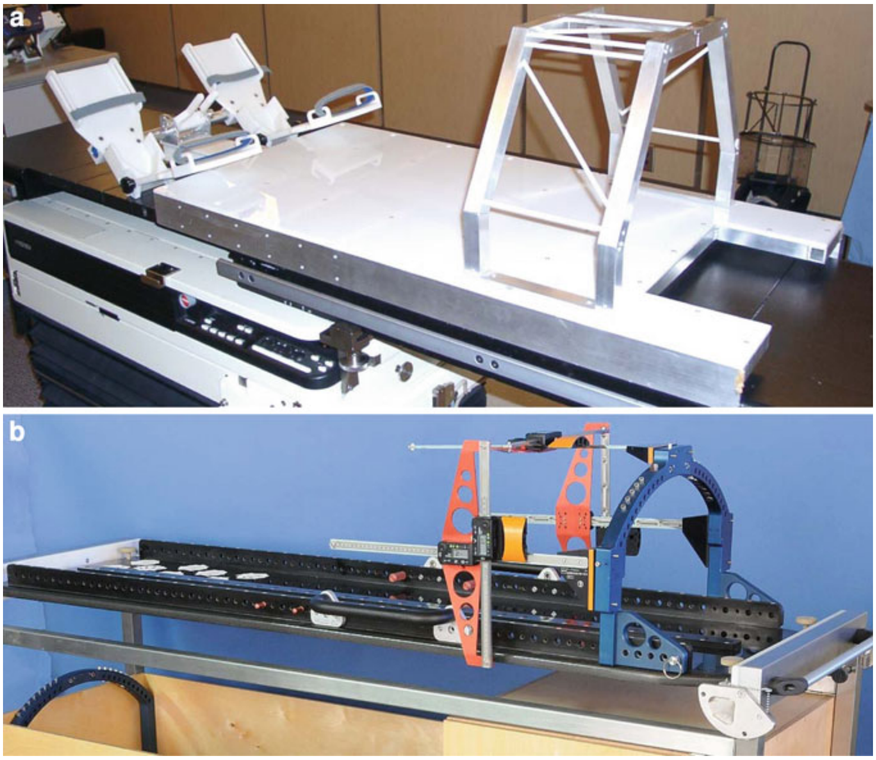

Fig. 13 **a** An early body frame design constructed by the UCLA group; **b** a commercial body frame (Leibinger), originally designed by the Heidelberg group

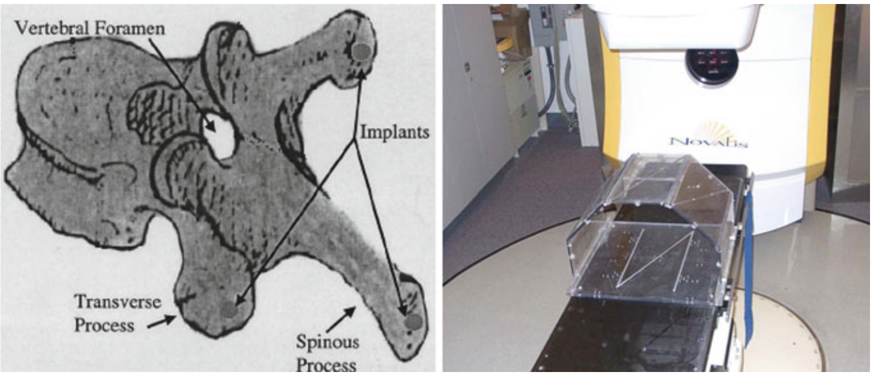

Fig. 14 The spinal radiosurgery approach described by Medin et al combined frame-based localization with kV projection image guidance using a mobile radiography unit

be performed despite the fact that (a) the patient had moved from the time of the initial CT and (b) the target could not be directly visualized in the treatment room. In phantoms specially constructed to evaluate overall system accuracy, the worst case targeting error observed was 1.17 mm. The methodology was subsequently evaluated in a swine model. Radionics briefly considered commercializing the methodology.

Two groups have combined in-room CT imaging with linac delivery for stereotactic irradiation of intra- and extra-cranial targets. A system combining in-room CT with fiducial-based localization for spinal radiosurgery has also been described by Shiu et al (2003). Patients were immobilized in a full-body stereotactic frame and received localization/verification CT scans immediately prior to treatment. This was facilitated by a CT-on-rails installed in the treatment room. With daily CT imaging, the authors determined the overall deviation from intended isocenter was within 1 mm for each treatment. Capabilities were later developed to facilitate automated registration of digitally reconstructed radiographs (DRRs) generated from the pretreatment CT scans to DRRs generated from the planning CT (Wang et al. 2007). Uematsu et al. (1996) reported on the treatment of eight patients with primary or metastatic brain tumors. Immobilization was performed using conventional head masks coupled with a dental impression. Localization was achieved by aligning the target to the axis of the CT gantry, marking the corresponding axes with small metallic balls, and subsequently aligning the metallic balls to the lasers of the linear accelerator. Phantom studies showed localization uncertainty on the order of 1 mm. Subsequently, the system has been used extensively for stereotactic targeting of extracranial tumors (Uematsu et al. 1998, 2000).

6.2 Stereophotogrammetric Methods of Stereotactic Localization

Stereophotogrammetry is the general term applied to the science of 3D measurement from two or more overlapping two-dimensional (2D) images. By obtaining images from at least two different locations and measuring the same target in each picture, a "line of sight" is developed from each camera location to the target. If the camera location and direction are known, the lines can be mathematically intersected to produce the 3D coordinates of each targeted point. The use of stereophotogrammetric techniques for localization of patients undergoing radiation therapy was first described by Schlegel et al. (1993) and Menke et al. (1994). They employed video stereophotogrammetry as a means of evaluating the repositioning accuracy of a specially designed head holder for fractionated radiotherapy. Shortly thereafter, Bova et al. (1997) adopted the methodology for cranial radiosurgery. The SPG method was sensitive enough to detect 0.05 mm deflections in a radiosurgery head holder.

In 1999, the group at the University of Chicago developed a video-based system for patient positioning (Johnson et al. 1999). The system used two CCD cameras to display real-time subtraction images for analysis of misalignment of head and neck patients. The authors showed that uncertainty could be significantly reduced (from 1σ of 5–7 mm to 1σ of 1–3 mm) if the system was used for online setup correction. More recently, optical systems have seen a resurgence in interest with the emergence of a commercial technology that uses optical techniques for real-time 3D surface tracking. (AlignRT, VisionRT Ltd., London, UK). While most clinical applications have focused on partial breast irradiation, the system has been recently adopted for cranial stereotactic radiotherapy (SRT) and general SBRT applications (Lindgren-Turner et al. 2005; Cerviño et al. 2010; Peng et al. 2010). Results suggest that the system provides accuracy comparable with conventional SRT methodologies. Further, localization can be performed in a matter of a few seconds.

Investigators have also implemented infrared stereophotogrammetry for extracranial localization. Wang et al. (2001) described a method in which passive infrared-reflecting spheres were affixed to the chest and/or abdomen of radiotherapy patients (ExacTrac, BrainLAB AG, Feldkirchen, Germany). Phantom studies demonstrated that the position of each IR-reflecting sphere could be determined to less than 0.3 mm, though CT-based target localization introduced additional uncertainties, on the order of 3 mm at the 95% confidence level. Ultimately, issues of marker reproducibility and patient motion led the authors to conclude that the accuracy of surface-based IR techniques was inadequate for stereotactic applications.

Working with investigators at the University of Iowa, Bova and colleagues subsequently coupled their infrared-based navigation system with ultrasound image guidance to facilitate targeting of paraspinal tumors (Ryken et al. 2001). System applicability was limited to soft tissue tumors located on the dorsal aspect of the spinal column; disease involving the bony vertebrae, the most common site for metastatic spread, could not be localized due to inherent limitations of ultrasound imaging. The authors subsequently described the treatment of a single patient presenting with a recurrent metastatic squamous cell carcinoma at the level of T-11; a dose of 15 Gy was delivered to the 80% isodose line. Bayouth et al. (2007) subsequently coupled the IR-ultrasound system with a specially designed linac to facilitate cranial and extracranial stereotactic applications.

In a similar manner, Fuss et al. (2004) used the stereotactic ultrasound (BAT, Best Medical International, Inc., Springfield, VA) to target malignancies of the upper abdomen. Due to the challenge of visualizing many of these tumors directly on ultrasound, the authors described the use of adjacent vascular structures as surrogates for target position. They reported that the technique was useful in 95.8% of setups, a significant improvement from traditional ultrasound methodologies. Despite these advances, ultrasound imaging remains challenging in the vast majority of tumor sites, and the use of stereotactic ultrasound is now largely restricted to applications in prostate cancer (Chinnaiyan et al. 2003; Fuller et al. 2006; Peignaux et al. 2006).

6.3 Orthogonal kV Localization (X-Ray Stereophotogrammetry)

The principles of stereophotogrammetry can be readily extended to X-ray imaging for direct visualization of internal anatomical structures, with the accuracy necessary for stereotactic applications. The application of X-ray imaging in stereophotogrammetric analysis (also known as Roentgen stereophotogrammetry) was first described by Selvik and colleagues (Selvik 1990; Johnsson et al. 1992; Axelsson et al. 1996).

Shirato et al. (1999, 2000) and Shimizu et al. (2001) described a system consisting of three room-mounted X-ray tube—image intensifier pairs, used for both localization and tumor tracking. The use of three imaging systems allowed for continuous 3D imaging, regardless of the position of the gantry position, which could obscure only one pair at a time. Continuous tracking was facilitated through the use of an implanted gold marker, which was recognized automatically using a pattern matching algorithm. The imaging system was synchronized with linac, with an uncertainty between intended and delivered target on the order of 1 mm.

Presently, both the CyberKnife and Novalis commercial systems provide room-mounted stereophotogrammetry capabilities coupled to their respective SRS/SBRT linacs. Because the imaging system is permanently mounted in the treatment room, targeting can be performed without the need for additional "localization boxes." The CyberKnife has two ceiling-mounted diagnostic X-ray units projecting through the patient to two opposing amorphous silicon detectors recessed within the treatment room floor. The biplanar imaging system provides capabilities for frameless stereotactic radiosurgery (Murphy 1997), and Initial CyberKnife applications were for the treatment of cranial disease, treated in a single or multiple fractions (Adler et al. 1999). However, the integrated image guidance system employed by the CyberKnife also makes it suitable for stereotactic irradiation of treat extra-cranial tumors. Murphy et al. (2000) have described modifications to the original CyberKnife to facilitate stereotactic irradiation of spinal and other tumors adjacent to rigid bony anatomy. Clinical applications of CyberKnife technology have grown rapidly, and many investigators have now reported their clinical experience in spine, lung, liver, pancreas and other extracranial sites.

Similarly, the Novalis system incorporates stereoscopic X-ray component for localization of extracranial targets with an infrared (IR) component to facilitate patient setup and allow for patient position monitoring. In contrast to the CyberKnife, the kV X-ray component consists of two floor-mounted X-ray tubes and two opposing amorphous silicon (aSi) flat panel detectors mounted to the ceiling. Each X-ray tube/detector pair is configured to image through the linac isocenter with a coronal field of view of approximately 18 cm in both the superior-inferior (S–I) and left–right (L–R) directions at isocenter. The X-ray localization system can be operated in two modes: matching of implanted radio opaque markers and automated registration of X-ray and digitally reconstructed radiographs (DRRs) using an iterative edge matching algorithm. Comprehensive evaluations of targeting accuracy have been reported by Yan et al. (2003).

6.4 Volume-Guided Localization

In-room volumetric X-ray guidance, specifically kV and MV cone-beam CT, has become commonplace in radiotherapy. Cone-beam CT is now a widely utilized modality for localization of SRS and SBRT patients (Fukuda 2010; Kim et al. 2011; Galerani et al. 2010; Worm et al. 2010; Wang et al. 2010). The initial experience is briefly described here.

Two groups from Germany successfully implemented kV cone-beam CT localization for intracranial radiosurgery and extracranial stereotactic body radiation therapy treatments. Boda-Heggemann et al. (2006) used volumetric kV imaging to assess the positioning accuracy and reproducibility in 21 patients undergoing cranial or head and neck irradiation. Automatic 3D–3D matching was used to register cone-beam images to the planning CT. While the study addressed only conventional versus cone-beam localization (i.e., there was no absolute reference on which to judge cone-beam localization itself), the authors nevertheless concluded that their experience supported a paradigm shift to purely image-guided setup for all intracranial precision radiotherapy procedures. Subsequently, Guckenberger et al. 2007a, b) used kV cone-beam CT for localization of patients receiving stereotactic radiosurgery for the treatment of brain metastases. They concluded that frameless radiosurgery based on image guidance with registration of the bony anatomy could be performed accurately and efficiently.

The same group has extended their cone-beam CT localization approach to SBRT treatment of lung tumors (Guckenberger et al. 2007a, b). Cone-beam CT imaging was determined to be of value in evaluating intrafraction variation in tumor position as well as for minimizing setup errors. Based on their analysis, the authors suggested that a 5 mm isotropic ITV-to-PTV margin was sufficient to account for intra-fraction effects. Duggan et al. (2007) used a similar localization technique in SBRT of lung cancer patients, incorporating deep inspiration breath hold for both the reference and cone-beam CTs.

Chang et al. (2007) evaluated the accuracy of kV cone-beam localization relative to fiducial-based stereotactic targeting. In phantom studies, an uncertainty in the cone-beam CT setup procedure of 1.34 ± 0.33 mm was observed. The investigators concluded that localization based on cone-beam CT image guidance was equivalent to that of currently used frame-based stereotactic radiosurgery systems. Letourneau et al. (2007) have developed a phantom for end-to-end dosimetric and geometric accuracy testing of cone-beam image guidance radiosurgery-type applications. To evaluate their methodology, a treatment plan was designed for single fraction radiosurgery of a spinal target. Image-guided setup was performed, and the phantom was irradiated according to the treatment plan. About 97.1% ± 1.5% of measurement points were within 3% of the calculated dose or within 2 mm distance to agreement.

6.5 Future Developments in Image-Guided SRS and SBRT

Future developments in image-guided SRS/SBRT will focus on two essential lines of investigation: continued improvement of imaging and delivery technology, and the radiation biology of large doses per fraction. While the latter is beyond the scope of this chapter, it is important to note the rapidly growing body of work in the development and application of preclinical stereotactic irradiation (DeSalles et al. 1996; Sun et al. 1998; DeSalles et al. 2001; DesRosiers et al. 2003; Jahan et al. 2006, 2007; Stojadinovic et al. 2006, 2007; Lotan et al. 2006; Walsh et al. 2006; Graves et al. 2007; Deng et al. 2007; Matinfar et al. 2007; Wong et al. 2008; Solberg et al. 2008; Matinfar et al. 2009; Saha et al. 2010; Cho et al. 2010; Zhou et al. 2010; Song et al. 2010; Medin et al. 2011).

With regard to technology, two devices have been recently proposed that provide tighter integration of imaging and delivery components. In 2006, a collaboration between scientists at three Japanese universities and institutes, working together with engineers at Mitsubishi Heavy Industries, Ltd. (Tokyo, Japan), constructed a next-generation system with capabilities for 2D and 3D localization and real-time tumor tracking (Kamino et al. 2006, 2007a, b; Takayama et al. 2009). A 6 MV C-band linear accelerator and micro-multileaf collimator are mounted on a computer-controlled gimbal which allows the linac to pan and tilt; an opposing flat panel provides beam-eye-view electronic portal images. The imaging subsystem consists of 2 kV sources and opposing detectors and can be operated in stereoscopic mode (radiographic or fluorographic) or can be rotated during image acquisition for reconstruction of volumetric (cone-beam) images. A cone-beam CT data set can be acquired in as few as 16 s. All components are housed in an O-ring gantry approximately 3.3 m in diameter which can rotate 360° about the table axis. The entire O-ring gantry can also rotate ± 60° about a vertical (skew) axis.

In April, 2010, Varian announced a new linac, TrueBeam^{TM}, with a significant redesign of major components, including the accelerator, bending magnets, flattening filters and carousel assembly and beam control systems. Further, the control systems allow sequencing and automated control of the couch, gantry and collimators with both on-board imaging and delivery (Lovelock et al. 2010). One of the most unique characteristics in the addition of flattening filter-free (FFF) photon modes, which generate dose rates of 1,400 MU/min and 2,400 MU/min at 6 and 10 MV, respectively. The FFF modes are well suited to stereotactic applications, as the beam profile is relatively flat for small fields (Naqvi et al. 2010). A detailed analysis of dosimetric characteristics of both standard and FFF modes has been provided by Hrbacek et al. (2011). The standard mode photon beams are clinically interchangeable with the Varian C-series linacs (Naqvi et al. 2010), and modeling of both the standard and FFF modes is accurately accommodated by the AAA algorithm of the Eclipse treatment planning system (Hrbacek et al. 2011). The TrueBeam is available in two configurations: with the standard Millennium MLC (0.5 cm wide leaves), or as the TrueBeam STx, with the HD-120 MLC (0.25 cm wide central leaves).

7 Conclusions

Stereotactic radiosurgery, with roots over a century old, has become a standard of care in the management of cranial disease. The success of SRS has subsequently stimulated application in extracranial disease sites. Just as SRS revolutionized the practice of neurosurgery, SBRT is now challenging conventional wisdom with regard to the practice of radiation oncology. This paradigm change has been facilitated in large part through technological development which continues to this day. Future development, in combination with a better understanding of the biological response to large dose-per-fraction irradiation and molecular approaches to optimize response ensure that SRS and SBRT will play an increasingly important role in the treatment of cancer for decades to come.

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