# Chapter 2
# History and the Technological Evolution of Stereotactic Body Radiotherapy

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**Abstract** After the discovery of use of therapeutic radiation, tremendous advances have been made towards targeted radiation. 3D conformal and intensity modulation have led to conformal therapy minimizing normal tissue toxicity. Improvements in diagnostic technology in delineating tumors, complex planning algorithms, robotic tracking devices, and megavoltage and particle beams have led to use of ablative radiation in the body with minimal side effects.

**Keywords** Stereotactic radiosurgery • Extracranial • Hypofractionation

## 2.1 Introduction

Traditional radical radiation therapy delivery requires multiple fractions of 1.5–3 Gy administered daily over a period of 3–7 weeks. These regimens have been derived and calculated from widely accepted models of the radiobiological effect of X rays on human tissue. However, hypo-fractionated, or even single large dose fraction treatments, were practiced in early days of application of X-rays in the treatment of cancer. It has been observed that large doses per fraction were tumorcidal, especially for epithelial tumors, but early clinical experience provided also lessons regarding the balance between tumor control and normal tissue toxicities. Early evaluations of radiation therapy showed that the delivery of large dose per fraction treatments was leading to unacceptably high acute and consequential late normal tissue toxicities. Therefore, quite early in the development of radiation therapy these schedules were abandoned because of complications such as fibrosis, stenosis, and vascular injury. Data collected at the initial stages of the development of radiation therapy supported the understanding that large dose single fractions lead to unacceptable treatment complications.

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The ability to manage the parameters underlying the unfavorable results for large dose per fraction therapy was severely limited in the early days of radiation therapy by the immature technologies of dose delivery. Particularly unfavorable were the relatively low energies of external beams used in the therapy. They were responsible for delivering large doses to normal tissues that were situated between skin and the target. These early experiences and their impact on the acceptance of particular fractionation schemes have been largely forgotten by later practitioners of radiation therapy, even when the megavoltage energies started to become available in radiation therapy. The paradigm of delivering a dose in small daily fractions has been taken for granted, and disconnected from the reflection that early treatments suffered multiple dosimetric limitations resulting from inadequate physical parameters of beams and unsophisticated therapy delivery technology. The exception to this was the treatment proposed by neurosurgeons in the Karolinska Institute; Dr. Leksell, inspired by the availability of high energy, megavoltage Cobalt beams, designed the radiosurgical treatment technique for brain known as Gamma Knife. The technique was not only utilizing the ability to move highly energetic photons to the targeted tissue in brain without depositing excessive energy to cells located between beam entrance at the skull surface and the target, but also relying on the relatively small separation distance between target tissue and the skull surface, and on limiting dose to healthy tissue by moving photons concentrically on the target from many directions (using 201 Cobalt sources).

Characteristic of this technique was that volumes exposed to high dose were relatively small in comparison to the total mass of brain tissue and delivered with high geometrical precision to targets (brain structures have fixed position relative to the skull). These properties of permanent localization of brain structures relative to the skull were helping to achieve the high accuracy of dose delivery when assisted by precise fixation of the skull relative to the Gamma Knife focus through a frame attached surgically to the patient's skull. The precision achieved by the attachment of the frame to the skull made it very inconvenient to irradiate brain in multiple fractions; therefore the regime of single fraction treatment was established for this radiosurgical procedure. The single fraction treatment made radiation oncologists who were practicing multi-fraction radiotherapy delivery skeptical about the radiosurgical treatment mode. Nevertheless, positive outcomes of these treatments accumulating over many years of clinical use of the technique (high success in target ablation and relatively small treatment toxicity with limited and manageable complications) gave enough evidence to reconsider the paradigm of multi-fraction treatments in radiotherapy.

Attempts to transfer the Gamma Knife experience to extracranial treatments were tried in Karolinska. However, initial attempts to transfer Gamma Knife experience to extracranial sites exposed differences in both therapies that pose technical difficulties [1].

First of all most extracranial structures are not fixed in position relative to the skin and so having information about location of the body surface relative to accelerator focus (isocenter) does not guarantee that the target is precisely positioned

relative to irradiating beams. Moreover, extracranial organs are moving both interfraction and intrafraction, and so their location at treatment may be different from their location at simulation and planning, even if we were able to reproduce the position of the target relative to machine focus with perfect precision before treatment was initiated. Therefore therapy practitioners who wanted to transfer cranial radiosurgery experience to extra cranial targets faced considerable technical challenges. The precise positioning of the target in the isocenter of the machine required setting a target by coordinate system derived from imaging of the body, together with verification that body geometry during treatment was close to identical to body geometry at the time of simulation and planning. Finally, there was a clear indication of the need for elimination, or significant suppression at least, of the body structures motion during treatment.

These conditions were to a large degree achieved by the body frame designed for this treatment in Karolinska by Drs. Henrik Blomgren and Ingmar Lax [1]. A treatment technique for extracranial radiosurgery was thus proposed by these researchers. The body frame allowed comfortable repositioning of the patient's body relative to the frame, equipped with metallic fiducial markers determining the system of coordinates relative to the frame geometry that was easily and accurately localizable relative to the room coordinate system of the simulator and the treatment accelerator.

The abdominal compression attached to the body frame allowed for minimization of respiratory motion of the organs within the chest and abdomen. Reproducible positioning of the patient's body with respect to frame assured, after accurate placement of the frame within the room system of coordinates, close correlation between treatment room system of coordinates of the target and organs at risk relative to accelerator isocenter and relative to spatial geometry of treatment beams.

Rescanning patients before each treatment fraction assured moreover the geometry of the body at treatment conformed to the body geometry at simulation and planning as referred to the body frame. Application of abdominal compression made the breathing motion small enough to keep margins around the target from 5 to 10 mm guaranteeing the volume of high dose exposure to be small. To keep the volume of normal tissues exposed to high dose per fraction in extracranial radiosurgery small, the original recommendation for hypofractionated treatment was to not treat targets exceeding 7 cm diameter. The final recommendation of Karolinska clinicians was that multiple beams converging on the target are used to concentrate high dose volume only in the target and its close vicinity. Following these recommendations assured that the dose distribution in extracranial radiosurgery was similar with standards of dose distribution utilized by Gamma Knife intracranial radiosurgery. These properties of extracranial dose characteristics gave them the confidence of recommending hypofractionated treatment, following the experience of Gamma Knife cranial radiosurgery. Generally three to five fractions (ranging between 8 and 20 Gy. per fraction) were used for extracranial radiosurgery with these characteristics. To obviate radiobiological uncertainties, these treatments were recommended initially for targets situated in parallel organs such as lung and liver.

## 2.2 Clinical Evolution of SBRT

The early extra cranial radiosurgery (now called – stereotactic body radiation therapy – SBRT) that followed guidance from the Karolinska group required considerable effort from radiation oncologist, radiotherapy physicist, dosimetrist and radiotherapist to ensure the treatment conformed to all requirements considered necessary for successful therapy. To ensure success of the treatment it was necessary to (with CT or MRI) simulate the patient carefully within the stereotactic frame when the patient was immobilized with abdominal compression applied, and spatial parameters recorded that located the patient relative to the frame and estimated the motion of the target subsequent to abdominal compression. Treatment planning demanded the identification of target relative to internal fiducial markers determining the position of the target within the body frame coordinate system, and then application of multiple beams (including non-coplanar beams for minimization of volume exposed to over the threshold dose) as well as careful analysis of DVH, and limiting of dose to sensitive structures in the vicinity of the target.

Before each treatment the patient had to be placed cautiously in the frame to reproduce the position of the body relative to the frame as performed during simulation. Nevertheless, even perfect reproduction of the surface and body bony landmarks with respect to the stereotactic frame was not a guarantee of the same relation of the soft tissue target relative to the frame. Therefore, there was a need to verify position of the target location within soft tissue before treatment initiation, by rescanning the patient in the frame. The comparison of body images prepared for treatment with images at simulation had to be evaluated by the radiation oncologist who would then decide if the treatment with parameters derived at planning could proceed, or required correction in placement of the frame relative to treatment room coordinate system. The whole process of patient setup for treatment, excluding time of rescan lasted 30–40 min and when time of treatment was added (with many beams and the large number of monitor units characteristic for hypo-fractionated therapy), the entire process of one fraction of treatment took around 1 hour.

This relative inefficiency of treatment in SBRT has made many physicians sceptical about the potential of this technique to become mainstream. However, it is worth bearing in mind that typical SBRT therapy needs only 1–5 fractions for the completion of the full therapy, making it still efficient when comparison of the total time of therapy is performed between SBRT and traditional fractionation.

In the USA the first center that regularly applied SBRT technique in the treatment of patients was Indiana University Department of Radiation Oncology, where Dr. R. Timmerman who had abundant experience in cranial radiosurgical therapy endorsed with enthusiasm the idea of extracranial radiosurgery [2–4]. The technique was routinely used originally for lung cancer patients who volunteered for this irradiation when faced with the choice of being untreated (inoperable lung cancer) or risking the potential futility of traditional fractionation radiation therapy. When the results from the internal Indiana University protocol were positive (high local control with limited toxicities observed) the natural next step was to test the technique in multi-institutional protocols.

Therefore, being encouraged by results of internal protocol Dr. Timmerman's group decided to design a national protocol for lung cancer treatment with extracranial radiosurgery technique. The primary goal of the national protocol was initially a phase 1 dose escalation trial to establish the appropriate dose in three equal fractions to be delivered to tumor in the lung with the goal of target ablation, whilst preventing significant toxicity [5]. The trial results have shown that dose can be escalated to 18–20 Gy. per fraction (with total of three fractions) resulting in local tumor control exceeding 90 %. These results were difficult to ignore and interest in the SBRT technique caught the attention of radiotherapy practitioners in the USA. Similar advances were also being made in other countries [6].

## 2.3 Devices, Delivery System and Localization: Early Techniques and Technology

Fortunately these developments coincided with advances in radiotherapy image guidance that enabled SBRT treatment set up to be less complex than was initially required. The important development in treatment delivery was the routine use of cone beam CT installed on new generation linear accelerators.

Cone beam CT made it possible to verify soft tissue anatomy of the patient when located on the treatment couch, removing the need for moving the patient being prepared for treatment to CT or MRI simulator. This resulted in substantial time savings during patient setup for treatment, and eradicated potential errors in target shifts relative to frame when transporting the patient in the frame from CT to treatment room. On the other hand tissue motion management techniques and tools permitted physicians to have more confidence that the dose prescribed to the target would actually be delivered even if the motion of the target exceeded margins assumed at planning.

Another major hurdle which needed to be managed was addressing random and respiratory motion management. Tissue motion management tools most regularly used in radiation oncology and applied to SBRT are dampening respiration, as described above, respiratory gating, and live respiratory motion tracking as performed by CyberKnife. These techniques are not perfect and so abolishing completely the margin for the target when these tools are applied is risky. Breathing motion is not perfectly stable and reproducible in spatial domain. The gating window will therefore always carry a residual error margin; prediction of the position of the target on which tracking properties of the CyberKnife are based may slightly differ from the model derived by CyberKnife Synchrony software if respiratory motion exhibits irregularity. Nevertheless, if combined with abdominal compression these techniques give a better chance of delivering the dose to the target as prescribed for the treatment plan. They may also be applied in cases, with relevant margins defined, when abdominal compression is not applicable.

Thus existing motion management tools can give the physician more confidence that prescribed dose is delivered to the target and that body organs at risk will not

exceed radiation exposure beyond tolerance. However, one also has to keep in mind that gating increases the treatment time still further. Nevertheless, the inconvenience for patient and decrease in efficiency of this factor may also lead to diminished comfort, that in turn may contribute to body dislocation relative to frame resulting in decreased accuracy of treatment delivery. The other aspect that needs to be taken into account when treatments lengthen is the potential radiobiological consequence of the decreased average dose ratio of the treatment. These concerns have to be appropriately taken into account when gating techniques are included as standard in SBRT practice. Modern gating techniques employ dynamic collimation, fiducial based gating including radiofrequency beacons, and active breathing control.

The other aspect of technological progress in radiotherapy delivery in SBRT is the ability to modulate the dose delivery by IMRT. Here we note that this may not be an essential development for SBRT as it has been practiced originally. In the case of SBRT the primary concern was to concentrate dose on the target and minimize the volume of high dose exposure to normal tissue. Achieving this dose distribution has more to do with appropriate directing of radiation beams in space than with modulating beam intensity, when beam directions are fixed in space. Nevertheless, the advance of SBRT to target locations such as liver or pancreas, that are in extreme proximity to sensitive organs, may require shaping of dose clouds that minimize dose in organs at risk.

## 2.4 Radiobiological Rationale and Its Impact on SBRT Techniques

The crucial question that arises in SBRT is the rationale for its effectiveness. Taking into account that radiobiology is not an exact science, we cannot answer these questions with absolute certainty. However, convincing heuristic advice is possible and should address speculative doubts about the technique. First it is easy to convince radiation oncologists that 54 Gy in three fractions should be a potentially ablative dose. This statement is sustained by radiobiological modeling. More surprising is the result that delivering this extremely high dose to the target in just a small number of fractions allows avoidance of excessive toxicity.

At this point, we should mention that with targets irradiated in parallel tissue, it seems reasonable to expect that cells incapacitated by radiation are not necessarily debilitating the functioning of the whole organ [7, 8]. Cells removed or inactive in lung and liver can be replaced in their functions by other cells within these organs. The important concern is that the inactive or ablated cells do not constitute too large a portion of the organ. However, this concern is explicitly addressed by the conditions of SBRT therapy delivery.

The other aspect of radiobiology that seems unclear from the point of view of SBRT results is the similar effectiveness of the treatment for extensively different fractionation schemes. For example SBRT methods in Japan where fractionation differed from the US RTOG 0236 produced comparable clinical results [6]. The possible explanation of this is that the LQ model routinely applied for deriving

equivalent dose is not directly applicable to hypofractionated regimes. A more detailed analysis of these aspects has been provided in [9] where some evidence suggests that Japanese dose schemes were actually similar to fractionation schemes employed in RTOG 0236.

## 2.5 Evolution to Treat Other Sites

The critical question for the SBRT technique is its applicability to organs and sites that have not been systematically investigated so far. These questions are justified, as the rationale for SBRT was to a large extent based on the assumption that parallel organs can tolerate limited volume radiation damage without grave consequences for their function, and the overall health of the patient. The existing results indicate that SBRT should be a treatment of choice for lung (excluding targets located in close vicinity of the bronchial tree) and liver and spine.

The success in treatment of prostate cancer with SBRT depends clearly on different factors than the success of treatment of lung cancer with SBRT. The prostate has to be irradiated in SBRT to a large dose in small number of fractions, however, as it is not contained in a parallel functioning organ, the primary concern will be to avoid dose to sensitive organs rather than minimizing the volume of the dose cloud overall. It seems rather convincing that doses of 50–60 Gy in 3–5 fractions delivered to prostate should have a huge potential of controlling the disease, and the fundamental question is then if current delivery techniques allow limiting of dose to rectum and bladder to avoid unmanageable toxicities in these organs. It is somewhat unclear at this time to decide if the combination of optimal beam spatial directions, modulation of beam intensities with the goal of shaping the dose cloud to envelop prostate whilst properly avoiding rectum and bladder, and management of prostate motion, at the time of treatment can result in suitable avoidance of toxicity with adequate irradiation of prostate itself. There are at the present time further trials (such as PACER) that try to answer these questions. Currently SBRT experiences have been reported in almost all body sites in both primary and metastatic cancer.

## 2.6 Conclusion

SBRT is at the present time a proven technique of radiotherapy delivery for lung and liver and spine. It has definitive radiobiological and convenience advantages relative to traditional fractionation. Clinically it shows unprecedented success in local control (comparable to surgery). It effectively uses new advances in technology of radiotherapy delivery. It applies these tools only as frequently as the fractionation regime requires. This encourages them to be used at each fraction for enhancement of the precision of therapy delivery. The small number of fractions makes also very efficient use of equipment and human resources in radiotherapy departments, to provide more courses of radiation treatment to more patients within the same

amount of time. The shortened course of irradiation can make also easier planning of comprehensive cancer therapy involving, surgery, chemotherapy and radiotherapy. More clinical trial data and longer patient follow up is required to justify the use of this technique in the treatment of other organs (such as pancreas, breast and prostate) and a better understanding of underlying radiobiological principles.

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