



Special stereotactic radiotherapy techniques: procedures and equipment for treatment simulation and dose delivery

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ABSTRACT

Stereotactic radiotherapy (SRT) is a multi-step procedure with each step requiring extreme accuracy. Physician-dependent accuracy includes appropriate disease staging, multi-disciplinary discussion with shared decision-making, choice of morphological and functional imaging methods to identify and delineate the tumor target and organs at risk, an image-guided patient set-up, active or passive management of intra-fraction movement, clinical and instrumental follow-up. Medical physicist-dependent accuracy includes use of advanced software for treatment planning and more advanced Quality Assurance procedures than required for conventional radiotherapy. Consequently, all the professionals require appropriate training in skills for high-quality SRT.

Thanks to the technological advances, SRT has moved from a “frame-based” technique, i.e. the use of stereotactic coordinates which are identified by means of rigid localization frames, to the modern “frame-less” SRT which localizes the target volume directly, or by means of anatomical surrogates or fiducial markers that have previously been placed within or near the target. This review describes all the SRT steps in depth, from target simulation and delineation procedures to treatment delivery and image-guided radiation therapy. Target movement assessment and management are also described.

Key words: stereotactic radiotherapy; frame-based stereotactic radiotherapy; frame-less stereotactic radiotherapy; organ motion; image-guided radiotherapy; radiosurgery

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Introduction

Stereotactic radiotherapy (SRT) is a multi-step procedure with each step requiring extreme accuracy. Physician-related aspects include appropriate disease staging, multi-disciplinary discussion with shared decision-making on treatment, choice of morphological and functional imaging methods to

identify and delineate the tumor target/s and organs at risk (OARs), an image-guided patient set-up, active or passive management of intra-fraction movement, clinical and instrumental follow-up. Physicist-related aspects include use of advanced software for treatment planning and more advanced Quality Assurance procedures [1-5] than required for conventional radiotherapy. Consequently, all

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the professionals (i.e., physicians, technicians and physicists) require appropriate training in skills for high-quality SRT.

A “frame-based” SRT refers to the system of stereotactic coordinates which are identified by means of rigid localization frames. Although frames are still used even today, “frame-less” SRT developed out of technological advances in radiotherapy and image-guided radiation therapy (IGRT). The latter localizes target volumes directly, or by means of anatomical surrogates or fiducial markers that have previously been placed within or near the target [6].

This review focuses on the technical aspects of SRT. Simulation and delineation procedures are presented as well as target movement assessment and management. Finally, equipment for SRT, treatment delivery techniques and IGRT are also presented.

Sources of information

From outset through February 2021, Pubmed and the Cochrane library were searched for relevant literature about procedures and equipment for SRT simulation and dose delivery.

State of the Art

Simulation and delineation procedures

This section refers to the ASTRO/ACR guidelines relating to the quality of SRT treatments [7–10], (which were recently updated), and to the ICRU Report n. 91 [2, 11].

Patients should be immobilized appropriately for simulation and treatment delivery using, for example, thermoplastic masks or vacuum cushions, according to the target site and anatomic features [4, 11–19]. The simulation CT scan is performed in the treatment position (preferably with contrast medium at least, for example, for liver lesion/s). As targets are small-sized, CT slices should be ≤ 2.5 mm in thickness. Should fiducial markers be required, they should be implanted beforehand.

Additional images are often required for target volume and OAR delineation. The most suitable ones are derived from multi-modal, functional imaging systems such as multi-parametric magnetic resonance imaging (MRI) and PET-CT which are co-registered (rigidly or elastically) with simulation CT images.

Target movement assessment and management Simulation phase

During simulation target movement assessment and management are essential for mobile targets in, for example, the lung or liver. Procedures include four-dimensional computed tomography (4D-CT) or strategies for breathing control [20–22].

4D-CT assesses motion amplitude by acquiring and subdividing volumetric images in all respiratory cycle phases, thus providing accurate target volume contouring and minimizing expansion margins. Its accuracy depends on patient’s maintaining a constant breathing pattern. Images are processed in sets of individual three dimension (3D) images over time. Automatic volume segmentation, e.g. by means of the deformable image registration, is essential for mapping and contouring as 4D-CT images are about 10-fold more than a standard simulation CT scan. Once lesion differences in the respiratory phases have been estimated, contour definition, planning and assessment may be automated on the various data sets.

Several strategies for breathing control are available; the monitoring systems must be used during both the simulation and the delivery phases).

1. Breath hold methods:

- a) in the Deep Inhalation Breath Hold (DIBH), respiration is suspended during a predefined phase, as compatible with the patient’s respiratory capacity. There are several options, which differ in how respiration is interrupted.
- b) in the self-held breath hold the patient is told to carry out reproducible breaths, deep inhalations and then to stop breathing in a specific respiratory cycle phase. She/He must remain immobile for 10–15 seconds (i.e. the dose-delivery time, considering the target as fixed in position at this time-point). Instead of respiratory monitoring, the patient can press a switch when ready to hold breath, so that treatment can be delivered. When the patient switches off, the beam is disabled.

2. Optical surface imaging systems (i.e. Catalyst™, C-RAD, Uppsala, Sweden; RPM, Varian Medical Systems, Palo Alto CA) can be used as breath monitoring and dose release systems, with or without markers placed on patient skin. The patient voluntarily holds his/her breath during a specific respiratory cycle phase. The main advantages are that breathing is constantly moni-

tored and treatment is automatically interrupted if breath hold deviates from expected.

3. The Active Breathing Control (ABC) device automatically stops breathing at an appropriate time, making the pause in breathing more reproducible. It consists of a spirometer to measure respiratory flow that is connected to a balloon valve which blocks breathing. The operator specifies when the system is activated during the respiratory cycle; the respiratory signal is processed and the valve is inflated by a compressor, thus blocking the patient's respiratory movement for a certain time.

Delivery phase

The Tumor Tracking is another strategy for organ motion control which is specific for the delivery phase [20, 21]. This technique tracks the target in real time, repositioning the beam as it follows target movement. A model predicts tumor movement, taking latency in beam positioning into account. The beam is then repositioned in accordance with gantry-repositioning or scanning delays. Dosimetry is adapted to changes in lung volume and OAR location during the respiratory cycle. The tumor position must be identified as it is the basis of real-time tracking procedures. At present, there are three tumor localization techniques:

- fluoroscopic tumor imaging detects isolated lesions in high contrast to the background (e.g. target/s in the lung);
- implanted marker imaging quantifies tumor movement. Three or more markers are implanted and the distance between them monitored. Gold markers, frequently used for lung and liver lesions, are visible in fluoroscopic images. The technique may be linked to significant implantation-related risks like bleeding or pneumothorax.
- tumor position reconstruction by means of an external surrogate respiratory movement signal, e.g. the Synchrony™ Respiratory Tracking System, a subsystem of Cyberknife® (Accuray®, Inc., Sunnyvale CA). Infrared sensors on the patient's chest and abdomen monitor movement. The infrared tracking system automatically records sensor movements by means of very high frequency optical localization methods. Updated positions are transmitted to the control unit more than twenty times per second. To accurately pinpoint the tumor position, they are combined with in-

formation from two orthogonal X-ray images acquired every 10 seconds so as to avoid excessive radiation exposure and too high an activation frequency of the X-ray generator. The main advantage of this method is that patients breathe normally during the entire session, while the Cyberknife® robotic arm actively compensates for respiratory movement. The Synchrony technology was recently transferred to the Radixact™: a camera is mounted to the ceiling and monitors the position of light-emitting diodes placed on the patient's chest. The external movements are correlated with the target movements, as evaluated by X-ray images which are taken at pre-fixed intervals. Although fiducial markers can be implanted near the target, they are not mandatory. The main collimator and the multileaf collimator (MLC) leaves follow in real time the lesion movements, thus compensating for the respiratory motion. The Synchrony technology is mainly suitable for, e.g., lung and upper abdominal lesions such as those in the liver, kidney, or adrenal glands).

Dosimetric studies report that patient-specific compensation strategies safely reduced target volume margins [20–22].

If none of these strategies is available, a 3D-CT based internal target volume (ITV) is obtained by contouring the target on CT-scans that are acquired during inhalation, exhalation and free breathing, and by planning on the free-breathing scan.

Equipment for SRT, treatment delivery techniques and IGRT

SRT implementation and requirements vary significantly with the target site. It is not a single treatment technique or therapeutic modality as it uses different technologies and equipment to deliver the prescribed dose to very small volumes, which are often adjacent to OARs.

SRT treatment is generally delivered with photons using a traditional LINAC that is equipped to deliver advanced treatments and has an adequate IGRT system. It may also be delivered by advanced dedicated apparatus. Protons or other heavy particles may be used in selected cases.

IGRT is crucial for SRT accuracy. Indeed, modern IGRT visualizes the target immediately before (or even during) the SRT session, “matches” images of pre-treatment and simulation positions and corrects set-up errors and organ motion (“baseline

shift”) online with pre-set threshold levels for patient repositioning [2, 23].

LINACs deliver step and shoot static intensity-modulated radiation therapy (IMRT), dynamic IMRT with multiple static beams, IMRT with dynamic arcs (volumetric modulated arc therapy, VMAT) or with high-dose rate Flattening Filter Free (FFF). IMRT offers the advantages of concave dose distributions in all three spatial dimensions with optimal high dose conformation, even on irregularly shaped targets. Thanks to multiple entry angles and beam directions, low doses to the OARs are modelled precisely. The beam penumbra may be partially compensated, thus reducing field size by increasing fluence at target edges [24].

The VMAT technique provides a highly conformed dose. It is delivered continuously throughout gantry rotation, the speed of which is continuously modified. Movement of MLC dynamically shape the beam. The dose-rate is modified during treatment erogation. Compared with IMRT, continuous dose delivery (without interruptions to reprogram fields or arcs) has the additional advantages of reducing the number of delivered monitor units and shortening treatment times [24–28]. Treatment times are reduced even further with VMAT-FFF techniques, at very high dose rates.

Cone beam computed tomography (CBCT) is the IGRT system used in LINAC. Using an X-ray tube and external panel on the LINAC for image acquisition, a volumetric CT is obtained immediately before the treatment session. CBCT has recently been made available in intra-fraction mode during treatment delivery. Respiratory-correlated 4D-CT methods should be integrated with IGRT, when available (e.g., 4D-CBCT) [5].

The most advanced LINACs for encephalic and body stereotactic treatments are reported below.

1. Varian® Truebeam®/EDGE®: Varian® systems are equipped with a robotic table with 6 degrees of freedom and a 120 blade (5 mm or 2.5 mm) multileaf. As they perform IMRT and volumetric arc treatments they can deliver up to 2400 UM/minute. Tumors are tracked by means of the EDGE® optical verification system on the patient’s skin or the Calypso® system of transponders that are inserted directly into the patient [29].

The Novalis TX® treatment system is equipped with ExacTrac®, an on-board localization system

consisting of two infrared (IR) cameras, two kV X-ray tubes and a robotic bed. The IR cameras guide the baseline patient configuration through external IR markers on the skin. Planar Rx images are co-registered with 3D-CT images, using a 2D-3D image recording algorithm [30].

2. The SRT-dedicated Elekta® Versa HD®: Elekta® system is equipped with the 160 blade Multileaf Agility® (5 mm), provides a FFF energy that delivers up to 2400 UM / minute and is suitable for IMRT and volumetric arc treatments [31].

Tomotherapy® [32, 33], Radixact™ [34], Vero® [35], Cyberknife® [36], MRIdian® [37] and Elekta Unity® [38] are equipped with special features for imaging and irradiation geometry.

The Tomotherapy® system consists of a LINAC and a megavoltage imaging system mounted in the gantry head of a spiral CT. During treatment delivery, the 6 MV LINAC completes multiple 360° rotations around the patient, while the couch translates through the central hole of the system. The MV-CT imaging system (3 MV photons) generates computerized tomographic images in the treatment position, thus checking the position before each treatment session [32, 33].

The Radixact™, the next generation Tomotherapy System, uses for IGRT the MV-CT and the new “ClearRT™ Helical kVCT Imaging” (i.e. an X-ray tube and an opposite kV detector) which is fully integrated into the radiotherapy treatment system. As the X-ray system is mounted on a rotating gantry, images are reconstructed similarly to a spiral CT [34].

The Cyberknife®, is a compact LINAC mounted on a flexible robotic arm, with over 1200 irradiation positions. Its non-isocentric irradiation geometries, with multiple beams (6 MV photons) provide a very high dose conformation with maximum OAR sparing. The CyberKnife® robotic arm tracks target movements “online”. To compensate for respiratory movement, it is guided by fluoroscopic imaging, which is sometimes coupled to IR position sensors, without the need for rigid body immobilization systems. Fidelity markers are required for tracking soft tissue targets while bone anatomy is used for intracranial or paravertebral targets [36].

The Vero 4D-RT® consists of a 6 MV LINAC mounted on a circular gantry (“O ring”) which tilts vertically and laterally. It is equipped with two pairs of X-ray kV imaging systems and an elec-

tronic portal imaging device. It provides a wide range of techniques, i.e. conformational 3D, conformational dynamic arcs, IMRT static fields (both step and shoot and dynamic), and hybrid arcs (dynamic conformational fields + IMRT static fields). The Vero4D[®] system dynamically monitors target movement during irradiation, by means of the X-ray head on universal joints which adjusts the beam direction at any time in accordance with tracking changes. The IGRT system consists of a single X-ray tube for CBCT or X-ray tubes mounted at 45° to the gantry head which simultaneously perform static or fluoroscopic scans [35].

The ViewRay[®] MRIdian[®] system consists of a LINAC with a 0.35 Tesla MRI-based IGRT system. The LINAC is equipped with a 138-leaf MLC, erogates beams with 6 MV FFF energy at 600 cGy/min dose rate and delivers IMRT and 3D-CRT plans. The new Elekta Unity[®] machine is equipped with a 1.5 Tesla “large bore” MR, associated with a 7 MV accelerator and a 160 blade MLC [37].

The ViewRay[®] MRIdian[®] and Elekta Unity[®] systems provide several advantages over CBCT due to better MR spatial resolution. During dose delivery, target position and movement are checked in real-time, therefore tracking the lesion during treatment. The system also includes on-board re-contouring and dose re-calculation software, making adaptive radiotherapy available for patients who are already positioned for treatment.

Unlike the above instruments, the Gamma-knife[®] [39] is suitable only for treating intracranial lesions. It was the first SRS-dedicated treatment system and the earliest reports date back to the 1960s (Karolinska Institutet, Stockholm, Sweden). The most recent version (Perfexion)[®] consists of about 200 sources of Cobalt 60 (gamma source with a 5.26-year half-life), connected to many metal collimators of different diameters which are driven robotically and focused on a common point (isocenter). The patient is connected up to the system by means of a stereotactic helmet that provides treatment coordinates and prevents intra-fraction movements. Accuracy is sub-millimeter, which is ideal for intracranial targets [40].

Varian Hyperarc[®] is also dedicated to intracranial radiosurgery. To Truebeam[®] and EDGE[®] accelerators it adds specific tools for single dose SRT, such as the brain module inside Eclipse[®], and the cot robot with 6 degrees of freedom (PerfectPitch[®]).

Together with various dedicated Aria[®] modules, it automatically distributes non-coplanar arcs to multiple isocentres [41].

Advantages and drawbacks of each equipment were reported in Table 1.

Conclusions and practical remarks

Interesting results emerged from studies comparing dose distributions with the various techniques to similar target volumes and contoured OARs [42–47]. One technique did not emerge as better than another and a large variability in mean doses to the target and OARs was due to different strategies for managing dose homogeneity (e.g. prescription isodose) [48–50]. Although many of these techniques perfectly conformed the prescribed dose to the target, low doses were diffused to the entire body. Recommendations include contouring all organs that could potentially be exposed to radiation, even when sited at a distance from the target.

Many parameters need to be considered when optimizing an SRT plan i.e., the TPS, dosimetric accuracy, prescription strategy and the team skills of physicians and medical physicists [51–54]. For comparison studies, uniform prescription criteria need to be established, shared and accepted by various Centers.

Adequate technologies for imaging and treatment delivery have made a major contribution to a widespread use of SRT. SRT treatment is generally delivered with photons using a traditional LINAC that is equipped to deliver these advanced treatments and has an adequate IGRT system. It may also be delivered by advanced dedicated apparatus. Protons have been tested; their use has been advocated as preferred treatment for larger and more complex lesions in order to reduce the risk of toxicity [55]. As very few studies have been published [56–59], research is needed before their selective advantages can be defined. Another innovative method for SRT is the PET-guided radiotherapy, or biology-guided radiotherapy, performed by the RefleXion[™] X1, a system that obtained the marketing authorization from the FDA in 2020. The radiotracer uptake, which converts the tumor itself into a biological fiducial for localization and delivery of a tracked dose, together with the rapid beam-station delivery, the real-time tracking, and

Table 1. Radiotherapy systems — advantages and drawbacks of each equipment

Systems	Imaging on board and positioning systems	Delivery systems	Type of radiotherapy system advantages and drawbacks
Varian® Truebeam®/EDGE®	Robotic table with 6 degrees of freedom IGRT (CBCT), Calypso system	IMRT, VMAT, 120 blade multileaf	LINAC based SRT and SRS <i>Advantages:</i> relatively low cost. <i>Drawbacks:</i> Need adjunctive system to tumor tracking
Novalis TX®	ExacTrac®: IR cameras, two kV X-ray tubes and a robotic bed CBCT	RapidArc, 120 blade multileaf	LINAC based SRT and SRS <i>Advantages:</i> Very accurate position evaluation
SRT-dedicated Elekta® Versa HD®	Robotic table, IGRT (CBCT)	IMRT, VMAT, 160 blade Multileaf Agility®	LINAC based SRT and SRS <i>Advantages:</i> relatively low cost <i>Drawbacks:</i> Need adjunctive system to motion control
Tomotherapy®	IGRT (MVCT)	IMRT delivery 360° sincronized with couch movement	LINAC spiral CT SRT <i>Advantages:</i> possibility to treat distant targets <i>Drawbacks:</i> Quality images of MVCT, long treatment delivery time
Radixact™	IGRT (MVCT and kVCT)	IMRT delivery 360° sincronized with couch movement	LINAC spiral CT SRT <i>Advantages:</i> possibility to treat distant targets, quality images of ClearRT™ helical kVCT imaging <i>Drawbacks:</i> long treatment delivery time
Cyberknife®	Fluoroscopic imaging guidance IR position sensors Fiducial markers	Tumor tracking with robotic arm	LINAC mounted on robotic arm <i>Advantages:</i> very accurate tumor tracking <i>Drawbacks:</i> complexity of the delivery, high diffuse dose (many non coplanar fields)
Vero 4D-RT®	IGRT: single X-ray tube for CBCT or X-ray tubes mounted at 45° to the gantry head, which simultaneously perform static or fluoroscopic scans	Conformational 3D, conformational dynamic arcs, IMRT static fields, hybrid arcs	LINAC mounted on a circular gantry <i>Advantages:</i> multiple solution to delivery <i>Drawbacks:</i> very complex delivery
ViewRay® MRIdian®	0.35 Tesla MRI-based IGRT system Possibility of intrafraction mobility check	IMRT 138 leaf MLC Possibility of adaptive recontouring	MRI-guided radiotherapy <i>Advantages:</i> high performance LINAC images, possibility of online replanning <i>Drawbacks:</i> costs
Elekta Unity®	1.5 Tesla "large bore" MR Possibility of intrafraction mobility check	IMRT 160 leaf MLC Possibility of adaptive recontouring	MRI-guided radiotherapy <i>Advantages:</i> high performance LINAC images, possibility of online replanning <i>Drawbacks:</i> costs
Gamma-knife®	IGRT: CBCT Possibility of intrafraction mobility check Uses stereotactic helmet that provides treatment coordinates	200 sources of Cobalt 60, connected to many metal collimators	Intracranial SRS system <i>Advantages:</i> High precision brain treatment <i>Drawbacks:</i> only for the brain targets, need high patient collaboration

IGRT — image-guided radiation therapy; CBCT — cone beam computed tomography; IMRT — intensity-modulated radiation therapy; VMAT — volumetric modulated arc therapy; SRT — stereotactic radiotherapy; IR — infrared; SRS — stereotactic radiosurgery; CT — computed tomography; MRI — magnetic resonance imaging; MVCT — megavoltage computed tomography; kVCT — kilovoltage computed tomography; MLC — multileaf collimator

the high-frequency multi-leaf collimation, allow a highly conformal treatment to the target and a significant spare of healthy tissues to be achieved. Furthermore, thanks to the use of a robotic couch with 6 degrees of freedom, multiple targets can be irradiated in a single session [6].

Technology in radiation therapy is continuously and rapidly evolving. Future studies in the field of SRT need to be conducted to assess whether a therapy unit offers not only technical (e.g. dosimetry, delivery, IGRT) advantages but also a better outcome.

Conflicts of interest

The authors have no conflict of interest to declare.

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