Original Contribution

Stereotactic body radiation therapy: 2007 update

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Stereotactic body radiation therapy (SBRT) consists of treating extracranial tumors with one to five highly conformal high-dose radiation fractions with ablative intent. SBRT has been made possible by the convergence of new body immobilization systems, improvements in radiation therapy planning algorithms that permit highly conformal isodose distributions, and the commercial availability of image-guided radiation units capable of delivering and verifying the spatial accuracy of such treatment. Several institutional phase I/II clinical trials designed to determine the maximal permissible doses and at least one cooperative group trial have been completed for tumors in the lungs, liver, and spine. Initial reports of efficacy in early-stage peripheral non-small cell lung cancer patients are encouraging, with 2- and 3-year local control rates ≥ 90% and low rates of grade 3 or higher toxicities (5%) being reported for high-dose treatments.

The potential to cure cancer with radiation was tested soon after the discovery of radioactivity and x-rays around 1900. Early treatment regimens using one or more high-dose treatments resulted in significant normal tissue late toxicity from stem cell depletion and decreased microvasculature with attendant fibrosis, sclerosis, ulceration, and necrosis. From these initial experiences, Coutard and Baclesse developed the concept of treating tumors with multiple low-dose fractions of radiation over several weeks, which results in less late normal tissue toxicity than more hypofractionated regimens providing the same total dose of radiation. These conventionally fractionated regimens have been used as the standard of care to treat the vast majority of cancer patients.

KEY POINTS

- SBRT is an ablative treatment of tumors designed to kill all cells in the target volume.
- High fractional doses of radiation kill greater numbers of cells than the same total dose delivered in more fractions.
- SBRT is best suited for the treatment of tumors situated in parallel tissue structures.
- The clinical implementation of an SBRT program requires rigorous quality assurance.
- Phase I/II clinical trials have established maximally tolerated doses for the treatment of tumors in the lung, liver, and spine. More clinical trials are under way or in development.

Lars Leksell, a Swedish neurosurgeon, hypothesized that intracranial lesions could be successfully treated with a single large dose of radiation with limited normal tissue toxicity if the head was rigidly immobilized and multiple beams were designed to converge on a small target volume; the proposed result would be that the target received a very high dose, with the adjacent normal tissues receiving a much lower dose due to steep isodose gradients.[1] He coined the term "stereotactic radiosurgery" for this type of treatment, and his pioneering vision led to the clinical development of the gamma knife at the Karolinska Hospital in 1969.

Innovations in software, hardware, and medical physics were required to provide suitable platforms for SBRT at extracranial sites. The development of robust 3-dimensional (3-D) treatment planning software allowing for complex CT-based radiation planning provided the dosimetric capability for creating highly conformal isodose distributions with multiple non-coplanar beams from a standard linear accelerator.

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One of the basic differences between intracranial and extracranial targets is that the extracranial tumor position and shape can vary due to patient motion, respiratory and cardiac motion, gastrointestinal peristalsis, bladder and rectal filling, and soft-tissue deformation. The steep isodose distributions created by 3-D planning systems required new patient immobilization systems and accurate tumor motion measurements to minimize the treatment margins necessary to account for the geometric uncertainty in tumor position and to prevent local recurrence from geographic target miss of the radiation.

Important events in the history of SBRT development include the following:

- 1994: Lax et al reported the first cases of stereotactic extracranial radiosurgery using an external body frame with a respiratory motion dampener.[2]
- 1995: Hamilton and colleagues developed a rigid spinal immobilization system that is surgically fastened to the spinous processes for spinal radiosurgery.[3]
- 1998: Uematsu et al reported the first Japanese experience with extracranial stereotactic radiation therapy for lung cancer patients.[4]
- 2001: Results of the first prospective phase I/II single-fraction SBRT dose-escalation trial for liver tumors are reported from Germany by Herfarth et al.[5]
- 2003: Timmerman et al reported results of an Indiana University phase I dose-escalation study of SBRT for medically inoperable early-stage non-small cell lung cancer patients.[6]
- 2006: Timmerman and colleagues reported results of a larger phase II study in the same setting.[7]

Radiobiology of stereotactic radiation therapy

Classic radiobiology principles and tenets were developed based on standard fractionation schedules, and many leading SBRT researchers are investigating whether these principles and the equations derived from them can be extrapolated to the dosimetric extremes of SBRT. The linear quadratic formula is the current mathematical model for describing the radiation dose cell survival curve for conventional radiation therapy. The linear quadratic formula predicts that a treatment of 60 Gy delivered in 3 fractions would be biologically equivalent to 180 Gy delivered in daily 2 Gy fractions Guerrero and Li[8] have proposed a modification of this formula for SBRT with the potentially lethal model initially proposed by Curtis[9] that accounts for the radiation repair that occurs during the radiation delivery; such repair results in much lower levels of cell killing than those predicted by the linear quadratic model, especially for protracted treatment times. Li's modified model is based on experimental data reported by Benedict et al[10] and Fowler et al[11] showing that prolongation of radiation delivery time results in loss of biologic effectiveness.

Since SBRT is an ablative therapy, conformality of dose is weighted much more than target-dose uniformity in the treatment planning process; this is so because toxicity with SBRT is related to high-dose spillage into adjacent normal tissues, and radiation hotspots within the target volume may be up to 50% higher than the minimum dose prescribed to the planning target volume. Since target volume dose homogeneity is more highly weighted in conventional radiation treatment planning, additional refinements to current radiobiology principles are necessary to account for the difference between SBRT and conventional fractionation in this regard.

The use of ablative radiation doses also limits most applications of SBRT to organs with parallel tissue structure as opposed to serial tissue structure. Parallel structures are redundant tissue structures in which all functional subunits perform the same physiologic functions independent of each other, such as the alveoli in the peripheral lung and the hepatocytes of the liver. In serial structures, the functioning of one functional subunit affects the functioning of the whole organ, as is the case with the spinal cord or bowel. Radiation injury to a small rim of normal lung or liver will have minimal consequences compared with radiation injury to the spinal cord, which could result in loss of function below the level of the spinal cord injury.

Clinical implementation of an SBRT program

There is currently no consensus regarding the exact requirements or specifications that define SBRT; several different conformality and dose homogeneity indices have been reported, making dosimetric comparisons between reported studies difficult. The American Association of Physicists in Medicine Task Force 101 on Stereotactic Body Radiation Therapy is currently reviewing commercially available SBRT-capable equipment and clinical reports and is formulating standardized dosimetric reporting definitions and quality assurance guidelines for SBRT. Until such guidelines are available, there are several major defining characteristics of SBRT that can be agreed upon[12]:

- Secure patient immobilization is needed to avoid patient movement.
- Accurate repositioning from simulation to treatment is necessary.
- Normal tissue exposure must be minimized through the use of multiple non-overlapping beams or large angle arcing small-aperture fields.
- There must be rigorous accounting for organ motion (abdominal compression, respiratory gating, respiratory tracking).
- There must be stereotactic registration.
- Ablative dose fractionation must be delivered with subcentimeter accuracy.

Multiple commercially available radiation units are capable of meeting the stringent localization and treatment requirements for SBRT;

the most common units include CyberKnife (Accuray), Novalis (BrainLAB), Synergy S (Elekta), Primatom (Siemens), TomoTherapy Hi-Art (TomoTherapy), and Trilogy (Varian). As shown in Table 1, the various units have different imaging capabilities, delivery techniques, and technologies for handling respiratory motion, but all have been used for SBRT.

With respect to reimbursement, CPT codes exist for SBRT. However, since many third-party insurance carriers currently consider SBRT to be experimental, it is critical to consult with individual carriers to determine which SBRT sites carriers will cover and to obtain appropriate preauthorization prior to the CT simulation. Availability of data on SBRT from large multi-institutional cooperative group trials will facilitate more widespread coverage of this treatment technique.

Summary of key clinical data

Lungs

To date, SBRT has been most widely studied in lung lesions. Prompted by the low local control rates of 30%–50% for T1N0 and T2N0 medically inoperable non-small cell lung cancer patients treated with conventionally fractionated radiation with 60–70 Gy in 30–35 fractions, researchers at Memorial Sloan-Kettering Cancer Center[13] and the University of Michigan[14] performed institutional phase I dose-escalation studies to determine the maximal permissible dose with standard fractionation; they were 84 Gy and 102.9 Gy, respectively. This was followed by the Radiation Therapy Oncology Group trial RTOG 9311, a phase I/II dose-escalation study in inoperable lung cancer patients, which reported a maximal permissible dose of 83.8 Gy.[15] These initial studies demonstrated that dose-escalation to 84–100 Gy was possible if specific lung dosimetric constraints were met. Despite these high total doses, local failure remained a significant problem, potentially reflecting accelerated tumor clonogen repopulation that occurs during prolonged radiation treatments of longer than 5–6 weeks' duration.

Timmerman and colleagues reported the results of a phase I SBRT dose-escalation trial for medically inoperable non-small cell lung cancer that enrolled 47 patients at Indiana University who were treated with only 3 fractions of radiation.[6] The maximal permissible dose was 60–66 Gy in 3 fractions for large lesions and was not reached for small lesions; the 2-year local control rate was 90% for patients treated with 18–24 Gy in 3 fractions. In a subsequent phase II trial in this setting, 70 patients were treated with 60 Gy for small tumors and 66 Gy for large tumors in 3 fractions.[7] The 2-year local control rate was 95%; toxicity was significantly higher for central lesions adjacent to serial structures, such as large bronchi, than for peripheral lesions located in parallel organ structures.

The RTOG has completed accrual to a phase II multi-institutional trial, RTOG 0236, in which 52 patients with medically inoperable non-small cell lung cancer with peripheral tumors less than 5 cm in diameter are being treated with 60 Gy in 3 fractions. The RTOG is planning three

TABLE 1

Characteristics of common radiation units suitable for stereotactic body radiation therapy

Manufacturer	Body SRT radiation unit	Image guidance	Respiratory management	Field collimation	Unit restricted to SRS?
Accuray	CyberKnife	Dual fixed x-ray; simultaneous imaging	Frameless real-time fiducial-based tracking	Circular cones only	Yes
BrainLAB	Novalis	Dual fixed x-ray; sequential imaging	Respiratory gating with IR markers	Micro-MLC with minimum of 3 mm at isocenter or circular cone attachments	No: field size limited to 10 × 10 cm at isocenter
Elekta	Synergy S	Rotating kV x-ray for fixed planar views and kVCBCT	Active breathing control (ABC): breath hold technique and frame/abdominal compression	Micro-MLC with minimum of 4 mm at isocenter or circular cone attachments	No: field size limited to 16 × 21 cm at isocenter
Siemens	Primatom	In-room CT scanner with couch coupled to LINAC	Frame/abdominal compression	MLC with 1-cm leaf or circular cone attachments	No
TomoTherapy	TomoTherapy Hi-Art	Fan beam MVCT	Frame/abdominal compression	Minimum MLC leaf configuration of 6 mm and 6-mm jaw width	No
Varian	Trilogy	Rotating kV x-ray for fixed planar views and kVCBCT	Respiratory gating with IR marker system	Micro-MLC with minimum of 5 mm at isocenter or circular cone attachments	No

CT = computed tomography; IR = inf
tion; MVCT = megavoltage computed tomography; SRS = stereotactic radiosurgery; SRT = stereotactic radiation therapy

additional non-small cell lung cancer SBRT trials:

- RTOG 0618 will enroll patients who are medically suited for surgical resection, with the rationale being that the local control rates observed thus far are comparable to those with lobectomy (85%–95%) and higher than those for wedge resection.[16]
- RTOG 0624 will include adjuvant systemic chemotherapy for patients at high risk of distant failure.
- RTOG 0633 will enroll patients with medically inoperable central tumors treated with a lower dose fraction schedule.

Institutional reports from Japan have also shown promising results using slightly lower SBRT doses. Uematsu et al reported a 94% local control rate with a median follow-up of 36 months for patients treated with 50–60 Gy in 5-6 fractions,[17] and Nagata and colleagues reported a 98% local control rate with a median follow up of 30 months for patients treated with 48 Gy in 4 fractions.[18] Neither of these studies reported any grade 3 lung toxicity.

Onishi and colleagues reported findings of a retrospective chart review involving 245 patients from 13 institutions treated with various dose fractionation schedules and found that the 2-year median local recurrence rates were 8% for patients treated with a biologic effective dose ≥ 100 Gy and 26% for those treated with a biologic effective dose ≤ 100 Gy.[19]

The RTOG of the Japan Clinical Oncology Group (JCOG) is currently enrolling medically operable (n = 65) and inoperable (n = 100) stage 1A non-small lung cancer patients to its phase II JCOG 0403 trial, a single-arm SBRT trial treating patients with 48 Gy in 4 fractions.

In summary, initial SBRT studies for non-small cell lung cancer report high local control rates of ≥ 90% with median follow up of 2–3 years for peripheral lesions that are less than 5 cm using dose fractionation schedules of 48–66 Gy in 3–5 fractions that result in minimal grade 3 toxicity. Stringent dosimetric and treatment delivery requirements are necessary to achieve these results. These local control rates rival those of lobectomy for similarly staged surgical patients, an observation that has prompted planning of cooperative group trials involving patients with operable disease. Central lesions carry higher risks of late toxicity due to their location near serial organ structures, with toxicity including bronchial damage with collapse or vascular damage. Radiographic changes of the lungs following stereotactic radiotherapy are common and include regional pneumonitis at 4–6 months with subsequent collapse of the distal lung and fibrosis at 9–12 months; PET CT may be required to differentiate fibrosis from recurrent tumor.

Liver

The majority of data to date for liver SBRT is for the treatment of oligometastases (one–three lesions). Herfarth et al reported a phase I dose-escalation study for the treatment of liver metastases from Heidelberg University, which enrolled 37 patients with tumor volumes of 1–132 cm^3 treated with single fractions of 14–26 Gy.[5] They reported an actuarial freedom from failure rate at 18 months of 67% and acceptable toxicity, with most failures occurring in the lower dose levels. Wulf et al reported a series of 23 patients from Würzburg University with liver metastases treated with 30 Gy in 3 fractions, with a 1-year local control rate of 76% and a 2-year local control rate of 61%.[20] Schefter and colleagues reported a phase I dose-escalation SBRT trial from the University of Colorado in which 18 patients with liver metastases received 36 Gy in 3 fractions up to 60 Gy in 3 fractions without reaching dose-limiting toxicity.[21]

In a phase II study, Hoyer et al treated 44 patients with colorectal metastases to the liver with 45 Gy in 3 fractions, reporting a 2-year actuarial local control rate of 86%.[22] In summary, preliminary data for SBRT of liver lesions have shown this treatment to be well tolerated with reasonable local control rates at 2 years.

Spine

Hamilton et al reported on a series of nine patients at the University of Arizona who had previously been irradiated to near spinal cord tolerance who were re-treated with a single 8–10 Gy fraction using a rigid spine immobilization system.[3] Chang et al reported an M. D. Anderson Cancer Center phase I study in 15 patients utilizing a CT on rails system with intensity-modulated radiation therapy for newly diagnosed and previously irradiated vertebral body metastases.[23] Patients were treated with up to 30 Gy in 5 fractions, with tumor doses limited by a maximum spinal cord dose of 10 Gy, and no neurotoxicity or grade 3 or 4 toxicities were reported. Ryu and colleagues reported on 61 solitary vertebral body lesions treated in 49 patients from Henry Ford Hospital with single fraction treatments of 10–16 Gy, with complete or partial pain relief being observed in 85% of the patients.[24]

The largest prospective non-randomized longitudinal cohort study of SBRT for spinal metastases was recently reported by Gerszten et al from the University of Pittsburgh.[25] In this study, 500 patients were treated with single fractions of 12.5–25 Gy (mean 20 Gy) with tumor volumes of 0.2–264 cm^3, with long-term tumor control of primary treated lesions being reported at 90%. SBRT for vertebral metastases with either a single fraction or up to 5 fractions can be delivered safely with high rates of pain relief and local control. Judicious patient selection and meticulous attention to treatment planning and delivery are necessary to avoid overdosing the spinal cord.

Conclusion

SBRT is becoming more widely

utilized. It is available at most academic centers and is being implemented by many community radiation oncologists on various treatment platforms. Early-phase trials in early nonsmall cell lung cancer, liver metastasis, and spinal metastasis reveal promising high initial rates of local control with 2–3 years of follow-up and minimal toxicity. Prospective multi-institutional cooperative group trials using standardized dosimetric reporting and quality assurance protocols are required for further advancement of the field and for broad-based acceptance of this treatment modality.

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