CHAPTER

24 Stereotactic Body Irradiation: Extracranial Tumors

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The success of stereotactic radiosurgery (SRS) for intracranial lesions spawned interest in applying the same principles of narrowly focused high-dose per-fraction irradiation in the management of selected extracranial tumors. The transition included an initial effort to design and implement a surgically placed rigid frame for spine immobilization,[1] but soon thereafter noninvasive means to target lung, liver, and other non-brain lesions were developed.[2,3]

Stereotactic body radiation therapy (SBRT) is the current American Medical Association Common Procedural Terminology (CPT) name applied in the United States to describe the management and delivery of image-guided high-dose radiation therapy with extracranial tumor-ablative intent within a course of treatment that does not exceed five fractions. Other labels that have been used in the past include extracranial stereotactic radiosurgery and various vendor-created nicknames, and a moniker that has been used in recent years is stereotactic ablative radiotherapy, which emphasizes the ablative potential of the treatment and has an appealingly onomatopoetic acronym (SABR). For simplicity the acronym *SBRT* will be used throughout.

In this chapter we review technical considerations, radiobiological implications, and normal tissue dose constraints for SBRT. Clinical outcomes after SBRT for common indications will be presented. The radiation physics of SBRT are discussed in a separate chapter in the textbook (Chapter 7).

SAFETY CONSIDERATIONS AND TECHNICAL ASPECTS OF STEREOTACTIC BODY RADIATION THERAPY

Relative to cranial SRS, the major additional practical hurdle that must typically be overcome to target an extracranial tumor with SBRT accurately and precisely involves accounting for breathing-related motion, present to some extent for nearly all cases apart from largely immobile spine and paraspinous tumors. Periodic breathing motion displacements have been both quantified and, if necessary, controlled with equipment and procedures used for simulation/planning and consistently applied toward treatment. Positioning errors (e.g., misalignment) either during a treatment or between treatments would also otherwise require expansion of targets. Numerous linear accelerator manufacturers now offer SBRT-ready treatment delivery systems that integrate a high performance linear accelerator with one or another form of image guidance technology, thus ensuring proper target relocalization and beam alignment. Collectively, these SBRT systems and procedures allow the use of considerably smaller fields compared with conventional radiation therapy without missing the target.

The American Society for Radiation Oncology (ASTRO) has issued guidelines on SBRT,[4] and the American Association of Physicist in Medicine (AAPM) Task Group 101 report expanded and augmented the ASTRO guidelines.[5] More recently, ASTRO also produced a white paper on quality and safety in SRS and SBRT.[6] In addition to describing the personnel and training requirements, the reports highlight key features of the quality assurance (QA) measures necessary to ensure the safety of the procedure.

The complete process of care for a patient receiving SBRT involves a multistep process that can involve patient immobilization, motion assessments (and motion-management if necessary), planning computed tomography (CT) image acquisition, analysis and processing of any four-dimensional image sets, fusion of the planning images with relevant diagnostic image sets, target delineation, dosimetric planning, patient-specific quality assurance testing, patient setup on the treatment couch, acquisition of guidance images to allow target relocalization, deployment of any motion-managing techniques or devices, proper initialization and commencement of the patient's unique beam and/or arc sequence, real-time monitoring of the integrity of the treatment delivery process, and the patient's stability and tolerance. At each step along the way are opportunities for systematic errors, miscalibrations, miscalculations, and any number of operator mistakes.

Regarding the possible purely technical sources of errors such as impaired performance of gantry motion or incorrect registration of pretreatment cone beam CT scans with the planning images in the image guidance software, careful initial commissioning and subsequent regular maintenance checks of individual components of the system are mandatory. Additionally, it is strongly recommended that there be end-to-end testing that incorporates all of the linked component parts to ensure that the additive impact of numerous small errors do not accumulate to a clinically relevant systematic targeting error whereby the planning target volume is not properly irradiated for any combination of reasons. The possibility of human error can never be completely eliminated. However, as noted in the chapter on stereotactic irradiation of central nervous system tumors, steps to reduce the chance of errors include the use of checklists and the development of a general culture of safety in which communication flows freely and nonjudgmentally among colleagues, with the common goal of quality patient care.[7]

SBRT requires proper patient repositioning, target localization, and management of breathing-related motion. Commercially available immobilization devices include several types of body frames with external fiducial markers, but these or any frameless system must always be used with accompanying image guidance that involves ultrasound, kV radiographs, CT scan, or magnetic resonance imaging (MRI) to verify the location of internal targets relative to the beams to be used (Figure 24-1). Because SBRT treatment sessions take more time than conventional external beam treatments, patient comfort is an important issue to lessen the chance that the patient might shift his or her position between the time of image guidance and treatment delivery.

Breathing motion management can be accomplished in one of several ways. Motion-dampening techniques involve light to moderate abdominal compression coupled with thoughtful patient coaching intended to transfer the predominant breathing forces from primarily abdominal (diaphragmatic contraction) to primarily chest wall (external intercostals, scalene, and sternocleidomastoid contraction). In this way, breathing forces

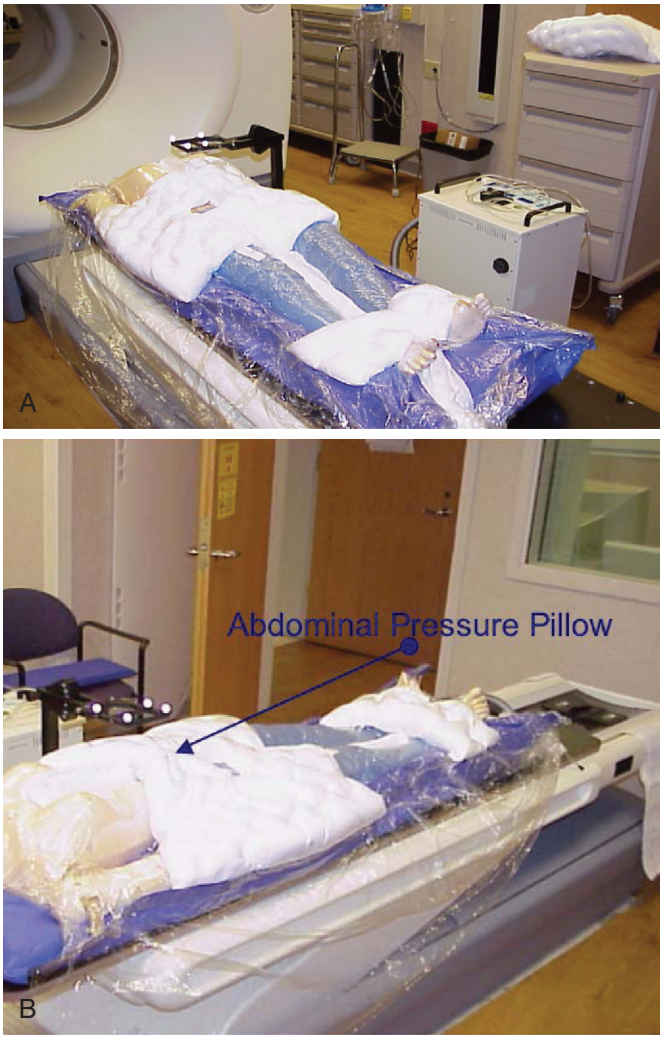

Figure 24-1 An example of a patient immobilization device for SBRT.

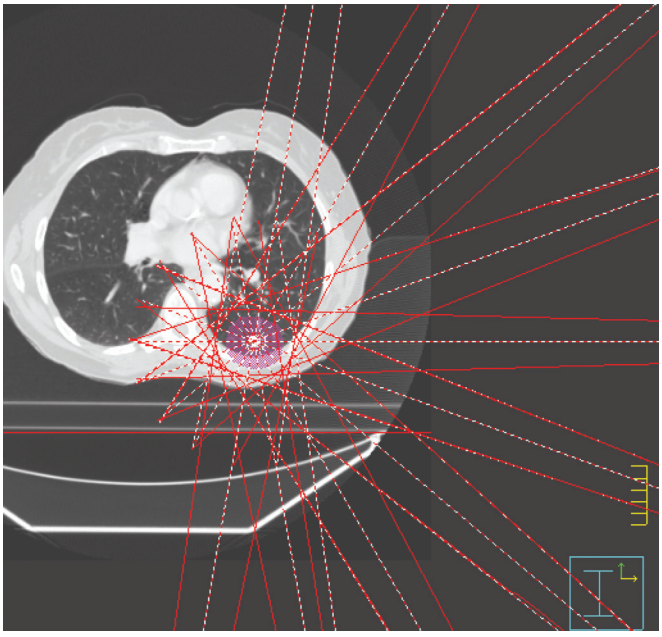

Figure 24-2 Typical beam arrangement and dose distribution for SBRT to a peripheral stage I lung cancer.

that otherwise put a tumor into motion with larger displacements are reduced while still facilitating an adequate tidal volume. Also within this category are coached breath hold maneuvers to "freeze" the tumor in space by drawing in and holding a constant tidal volume (e.g., deep inspiration) and holding that volume while the radiation beam is engaged. Gating systems may be used for SBRT in the same manner as for conventionally fractionated radiotherapy: the movement of external surface markers is correlated with phases of the breathing cycle, and beam output is triggered only when the markers are located within a preselected segment of the breathing cycle, implying tumor location within the expected range of motion. Tracking or "chasing" systems move the radiation beam to follow the movement of the tumor. Both breath hold and gating methods have a duty cycle whereby the beam is turned on and off for periods of time, thus lengthening the total treatment time. To some degree these motion management techniques can be used in conjunction (e.g., abdominal compression and gating) to reduce the overall target displacements or duty cycle.

Most clinical implementation of SBRT thus far has involved high-energy photons as the source of therapeutic radiation. However, charged particles could also be used. There is no absolute standard or consensus class solution for the combination of beam or arc angles best suited for any given clinical situation, and each case can present idiosyncratic challenges. In general, though, to achieve a tightly focused high-dose distribution within the planning target volume (PTV) and rapid dose fall-off outside the PTV, a combination of multiple (often 7 to 10) noncoplanar beams or multiple arcs is often required (Figure 24-2). Intensity modulation across the individual beams or arc segments can be incorporated within SBRT, but it is important to bear in mind that as for cranial SRS, it is typically advantageous to allow for a dose hotspot to accumulate inside the PTV to steepen the dose falloff outside the target, exploiting the natural gradient of the lateral beam penumbra to some extent in this regard. One notable exception to this practice would be in the case of prostate SBRT, where it is important to avoid a hot spot in the region of the urethra.

CLINICAL RADIOBIOLOGY AND NORMAL TISSUE DOSE CONSTRAINTS

The emerging knowledge about high-dose per-fraction irradiation is reviewed in more detail in the chapter on stereotactic irradiation of CNS tumors. Briefly, the mathematical models established to describe the relationship between radiation dose and biological effect in tumor and normal tissue that are generally reliable for conventionally fractionated radiotherapy are less stable in the setting of high-dose per-fraction irradiation. The linear quadratic model tends to overestimate the in vitro cytotoxicity of doses on the order of 8 Gy to 10 Gy or higher, and yet there is added uncertainty with regard to the in vivo effects of doses in this range because of the suspected extra effect of endothelial cell apoptosis, which can lead to tumor cell death via an early antiangiogenic mechanism as well as likely more late-fibrosing vascular effects. Given these caveats concerning traditional radiobiological models, for the purpose of predicting the effect of SBRT on tumors and normal tissues, it is best to rely whenever possible on empiric observations that relate dose or dose-volume parameters to directly observed rates of tumor control or normal tissue toxicity.

SBRT Dose versus Tumor Control

There are numerous reports that support the concept of a dose-tumor control relationship over the range of doses that have been explored for lung and liver SBRT. For example, McCammon et al reviewed the records of 141 consecutive patients with 246 lung or liver lesions treated with three-fraction SBRT regimens.[8] Lesions treated to a nominal dose of 54 Gy or greater had a 3-year actuarial local control rate of 89.3% compared with 59.0% and 8.1% for those treated to 36 Gy to 53.9 Gy and less than 36 Gy, respectively.

Similarly, Olsen et al reviewed the records of 130 patients who underwent definitive lung cancer SBRT to a single lesion, receiving 18 Gy × 3 fractions for peripheral tumors (n = 111) and either 9 Gy × 5 fractions (n = 8) or 10 Gy × 5 fractions (n = 11) for tumors that were central or near critical structures.[9] The observed local control after 1 or 2 years were, respectively, 75% and 50% for 9 Gy × 5, 100% and 100% for 10 Gy × 5, and 99% and 91% for 18 Gy × 3. No difference in local control or overall survival (OS) was found between the 10 Gy × 5 and 18 Gy × 3 groups, but treatment with 9 Gy × 5 was the only independent prognostic factor for reduced local control on multivariate analysis.

In yet another study that was particularly robust because of the structured dose escalation within a prospective trial, Rule et al treated patients with hepatic metastases in three consecutive dose-escalation cohorts: 30 Gy in three fractions, 50 Gy in five fractions, and 60 Gy in five fractions.[10] Twenty-seven patients, 9 in each cohort, with 37 lesions were enrolled and treated: 17 men and 11 women; median age 62 (range 48 to 86) years. The most common site of primary disease was colorectal cancer. The 2-year actuarial local control rates were 56%, 89%, and 100% for the 30 Gy, 50 Gy, and 60 Gy cohorts, respectively. There was a statistically significant difference for local control between the 60 Gy and 30 Gy cohorts (p = 0.009) but not between the 60-Gy and 50-Gy cohorts (p = 0.56) or the 50-Gy and 30-Gy cohorts (p = 0.091). Thus, taken together, the results of these studies support that SBRT doses in the range of 50 Gy to 54 Gy or higher in three to five fractions provide superior local control rates than less aggressive regimens for liver and lung lesions.

Normal Tissue Dose Constraints

There is a growing literature of reports characterizing SBRT dose-effect relationships in normal tissues, notably for liver, lung, and intestinal tissue. In an effort to analyze these data in aggregate to search for consistent trends across series, the AAPM has supported a working group initiative involving dozens of volunteers charged with cataloging all of the published SBRT studies that include clinical information, treatment details, and rates of toxicity. Although the results of this effort might eventually illuminate correlations not appreciated when only smaller numbers of patients in individual reports are considered, there are already strong indicators of effects that are routinely observed after high-dose per-fraction irradiation above given thresholds of dose or volume, some considered clinically harmless and others associated with toxicity.

One feature of the normal tissue effect of liver SBRT consistently observed within the first few months after SBRT is a zone of hypodensity observed on follow-up CT scans corresponding to the volume that received approximately 30 Gy in three to five fractions. This phenomenon, first described by Herfarth et al following single dose liver SBRT,[11] is related to a local veno-occlusive effect.[12] There is no clinical consequence associated with the finding per se, and it will resolve over time, but the Herfarth effect can obscure the assessment of tumor response within the first few months after liver SBRT. Of greater utility for this purpose would likely be a positron emission tomography (PET) scan, but here it should be appreciated that it will take months for the full effect of treatment to mature and lower the standardized uptake value (SUV) of target lesions.[13]

For conventionally fractionated radiotherapy, it has been observed that the risk of significant radiation-induced liver disease (RILD) characterized by ascites, anicteric hepatomegaly, and elevated liver enzymes is well correlated to the mean liver dose.[14] Fortunately, RILD is an exceedingly rare complication after liver SBRT because the mean dose to uninvolved liver parenchyma is generally well below what has been given in the past using conventional techniques. Indeed, normal tissue complication probability (NTCP) models established for conventional fractionation have not reliably predicted toxicity after liver SBRT, typically overestimating the risk.[15]

The QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) summary recommendations for liver SBRT given in a three fraction regimen are to constrain the mean normal liver dose (liver minus gross tumor volume) to less than 13 Gy for primary liver cancer and less than 15 Gy for metastases and to ensure that at least 700 mL of normal liver receive less than 15 Gy.[14] This latter recommendation is based on a so-called *critical volume model*. Relevant for organs of parallel structure, this construct requires recognizing how much volume of the organ is essential and must be protected from functional ablation. The estimate for liver that at least 700 mL should receive less than 15 Gy during a three-fraction SBRT course was originally derived from a combination of prior reports of outcomes after partial hepatectomy documenting approximate minimum volumes required and good faith estimates of the effects of that dose of radiation extrapolated from prior reports of conventionally fractionated treatment.[16]

Analogous to the Herfarth reactions after liver SBRT are observations of lung inflammation and fibrosis in and near the zone of high dose irradiation after lung SBRT. Diot et al studied post-SBRT follow-up CT scans of 62 patients who received lung SBRT prescribed to a median dose of 54 Gy (range, 30 Gy to 60 Gy) in three to five fractions. The surrogate marker of parenchymal injury was an increase in Hounsfield Units (HU), presumed here to represent postinjury scar tissue. Across a range of follow-up intervals, the HU values linearly increased with dose until 35 Gy and were constant thereafter. For 3, 18, 24, and 30 months, the rate of HU increase with per dose was consistent; however, at 6 months the rate was similar below 20 Gy but then doubled above this threshold, suggesting a phase of peak post-SBRT inflammation that subsides at later time points. These observations largely validated the quantitatively similar contemporaneous work of Palma et al, who also noted an independent effect on promoting lung fibrosis with larger PTV.[17]

Radiation pneumonitis, characterized clinically as cough, fever, shortness of breath and chest pain, and associated radiographically with a geometric alveolar infiltrate corresponding to irradiated volumes, is an uncommon event after lung SBRT. In the Radiation Therapy Oncology Group (RTOG) 0236 study in which patients with medically inoperable early stage lung cancer were treated with SBRT to a nominal dose of 60 Gy in three fractions (recalculated as 54 Gy in three fractions when accounting properly for tissue heterogeneity), the incidence of grade 3 radiation pneumonitis was 4%, with no grade 4 or 5 radiation pneumonitis.[18] A subsequent analysis of the same study documented no clinically significant changes in pulmonary function after treatment.[19] For a large cohort of patients treated at the M. D. Anderson Cancer Center, Chang et al found on multivariate analysis that only the mean dose to ipsilateral lung (lung minus gross tumor volume) was a significant predictor of grades 2 to 3 radiation pneumonitis after lung SBRT,

with a sharp increase in incidence when this metric exceeded approximately 9 Gy.[20] It has also been noted that tumor location might have a substantial influence on risk of toxicity, with a higher rate of severe toxicity observed for centrally located tumors in the initial Indiana University experience.[21]

The intestinal tract is a thin-walled structure that is susceptible to injury from high-dose per-fraction irradiation. For the major segments of the gastrointestinal tract studied to date (esophagus, duodenum, and rectum), the most significant predictor of post-SBRT late toxicity is a dose-volume metric whereby toxicity is triggered when the amount of tissue receiving a certain dose exceeds a threshold volume.[22-24] For example, in the esophagus, after a single fraction exposure, there is an escalated risk of grade 3 or higher toxicity if the volume receiving 12 Gy exceeds approximately 4 cc[22]; similarly, the risk for duodenal toxicity, grade 2 or higher, escalates sharply if the volume receiving a single fraction of 15 Gy exceeds approximately 9 cc.[23] In an analysis of a dose escalation study of prostate SBRT, the risk of grade 3 or higher late rectal toxicity was significantly elevated when the volume of rectal wall receiving 50 Gy exceeded 3 cc.[24]

CLINICAL INDICATIONS AND OUTCOMES

Lung Cancer

An important unmet medical need provided the impetus for much of the early development of SBRT. Until the advent of SBRT, a patient with medically inoperable stage I lung non–small cell lung cancer (see Chapter 44) would derive rather limited clinical benefit from conventionally fractionated radiotherapy (CFRT). The Surveillance, Epidemiology, and End Results (SEER) registry indicated a median survival of a little more than a year is typical without any radiotherapy, extending to approximately 21 months with CFRT, with an expected 3 year OS on the order of 30%.[25] The challenge for these patients was that CFRT did not achieve a high rate of local control and was poorly tolerated in a patient population especially susceptible to pulmonary toxicity. The typical single-institution analysis from centers of excellence revealed 3-year local control rates of approximately 50%, with consistently disappointing median survival of less than 2 years.[26,27]

Breakthrough improvements relative to this baseline were achieved in studies performed contemporaneously in separate multiinstitutional studies on two continents. In the Nordic Group study from Europe and the RTOG study from North America, SBRT was employed to treat patients with medically inoperable early stage lung cancer to a dose of 45 Gy to 54 Gy in three fractions, achieving a local control of more than 90% and a 3-year OS of approximately 60%.[18,28] These results are roughly twice what was typically achieved historically with CFRT, establishing a new standard of care in this setting.

In addition to its well-established role in medically inoperable early stage lung cancer, SBRT has gained traction as an acceptable approach for a variety of other indications. Primary prostate, pancreas, and hepatocellular cancers may be well treated with SBRT. Additionally, SBRT can serve as a noninvasive means of ablating oligometastatic tumor deposits in the lung and liver as well as controlling challenging para-spinal tumor deposits.

Prostate Cancer

King et al have reported tumor control outcomes and prospectively collected patient-reported quality of life effects in 1100 patients who had been enrolled in prospective trials and registries of SBRT for prostate cancer[29,30] (see also Chapter 53). The median follow-up was 3 years and 194 patients remained evaluable at 5 years. After a median dose of 36.25 Gy in four to five fractions, the 5-year biochemical relapse free survival rate was 95%, 83%, and 78% for patients with Gleason Score 6, 7, and 8, respectively, and 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively. A temporary decline in self-reported urinary and bowel function was observed within the first 3 months after SBRT which returned to baseline status or better within 6 months and remained so beyond 5 years. A decline in sexual quality of life was observed predominantly within the first 9 months, with no significant impact from androgen deprivation or patient age. SBRT for prostate cancer is less costly than other forms of radiation therapy.[31,32] However, an analysis of the experience of early adopters of this technology suggested there the rate of genitourinary toxicity after SBRT for prostate cancer might be slightly higher than for CFRT,[32] and so continued analyses of ongoing prospective studies will be important to understand what metrics are important for optimizing the quality of care in this setting.

Gastrointestinal Cancers: Pancreatic and Hepatocellular

Regarding the use of SBRT for locally unresectable pancreatic cancer, in an early Danish study, a large volume of bowel received a high dose (30 Gy or higher in three fractions), leading to substantial toxicity.[33] Learning from that experience, investigators from numerous institutions have reported the safe administration of SBRT to tightly focused fields around the primary pancreatic tumor, often sandwiching cycles of chemotherapy around the SBRT with minimal interruption of the chemotherapy, achieving survival and toxicity rates that compare favorably with CFRT[34-36] (see also Chapter 48).

Yet another domain in which SBRT has been explored is the primary treatment of hepatocellular cancer (HCC) (see also Chapter 49). Here, as for the other primary cancers noted previously, SBRT is an appealingly noninvasive therapy. SBRT can be administered either as definitive therapy or as a bridge to liver transplant.[37] In the Indiana University experience, 60 patients with liver-confined HCC were treated with SBRT to doses adjusted according to pretreatment liver function.[38] For Child-Pugh (CP) class A patients, the majority of patients received a prescription dose of 48 Gy in three fractions; in contrast, for CP class B patients, the dose was reduced to 40 Gy in five fractions. With a median follow-up time of 27 months for the 60 patients treated (36 CP A, 24 CP B), the 2-year local control, progression-free survival, and OS were 90%, 48%, and 67%, respectively. Twenty-three patients underwent transplant a median of 7 months post-SBRT. There was no grade 3 or higher nonhematologic toxicities, although 20% of patients experienced a progression in CP class within 3 months of treatment. This latter toxicity was similar to what was noted by the Princess Margaret Hospital group in their prospective studies.[39] In a large Japanese retrospective study, patients treated with SBRT had CP A or B status and a single primary or recurrent HCC lesion 5 cm or less in maximum diameter.[40] The prescribed dose was 40 Gy for CP A and 35 Gy for CP B, given in five fractions, with a dose reduction if more than 20% of the liver received more than 20 Gy. A 5-Gy dose reduction was required if the proportion of the liver receiving ≥20 Gy exceeded 20%. For the entire cohort of 185 patients (n = 48 in the 35-Gy group; n = 137 in the 40 Gy-group), the 3-year local control and OS rates were 91% and 70%, respectively.

Oligometastases

Ever since Hellman and Weichselbaum coined the term *oligometastases* and suggested a role for conformal radiotherapy in

this context,[41] there has been steadily increasing interest in ablating limited foci of metastatic disease radiotherapeutically or by other local intervention. A full discussion of this topic is beyond the scope of the present chapter, but there are numerous reviews summarizing the canon of literature that documents durable disease-free survivorship following surgery, radiotherapy, or other local ablative modality for many patients with limited deposits of metastatic disease.[42,43] A recent example of one of the evolving paradigms in which this approach appears to have a role is in the setting of oligoprogressive disease in a patient on therapy with a novel targeted agent, where the strategy is to "weed the garden" of resistant clonogens while extending the patient's access to an agent that is still providing systemic benefit. Gan et al described the use of local ablative therapy for patients with anaplastic lymphoma kinase-positive lung cancer receiving crizotinib.[44] Among 33 patients who progressed while taking crizotinib, those with progression outside the central nervous system (n = 14) received SBRT or equivalent local ablative therapy. The 6- and 12-month actuarial local lesion control rates with SBRT were 100% and 86%, respectively. Crizotinib was continued after local ablative therapy. The use of local ablative therapy allowed a longer duration of the use of crizotinib. Patients continuing to take crizotinib for >12 months versus ≤12 months had a 2-year OS of 72% versus 12%, respectively ($p < 0.0001$).

CONCLUSIONS

SBRT has emerged as a technology with the potential to benefit cancer patients in many ways. SBRT has an established role as a standard therapy for medically inoperable early stage lung cancer and is a viable alternative to surgery and other forms of radiation therapy for numerous other malignancies. There remain opportunities to refine the technical aspects of treatment delivery as well as our understanding of the ideal patients to treat.

CRITICAL REFERENCES

A full list of cited references is published online at www.expertconsult.com.

4. Potters L, Kavanagh B, Galvin JM, et al: American society for therapeutic radiology and oncology (ASTRO) and American college of radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 76(2):326–332, 2010.
5. Benedict SH, Yenice KM, Followill D, et al: Stereotactic body radiation therapy: The report of AAPM task group 101. Med Phys 37(8):4078–4101, 2010.
6. Solberg TD, Balter JM, Benedict SH, et al: Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. Practical Rad Oncol 2(1):2–9, 2012.
7. Marks LB, Jackson M, Xie L, et al: The challenge of maximizing safety in radiation oncology. Practical Rad Oncol 1(1):2–14, 2011.
11. Herfarth KK, Hof H, Bahner ML, et al: Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. Int J Radiat Oncol Biol Phys 57:444–451, 2003.
14. Pan CC, Kavanagh BD, Dawson LA, et al: Radiation-associated liver injury. Int J Radiat Oncol Biol Phys 76(3):S94–S100, 2012.
17. Palma DA, van, Sörnsen de Koste J, Verbakel WF, et al: Lung density changes after stereotactic radiotherapy: A quantitative analysis in 50 patients. Int J Radiat Oncol Biol Phys 81(4):974–978, 2012.
18. Timmerman R, Paulus R, Galvin J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303(11):1070–1076, 2010.
20. Chang JY, Liu H, Balter P, et al: Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non–small cell lung cancer. Radiat Oncol 7:152, 2012.
22. Cox BW, Jackson A, Hunt M, et al: Esophageal toxicity from high-dose, single-fraction paraspinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 83(5):e661–e667, 2012.
24. Kim DW, Cho LC, Straka C, et al: Predictors of rectal tolerance observed in a dose escalated phase I/II trial of SBRT for prostate cancer. Int J Radiat Oncol Biol Phys 89(3):509–517, 2014.
28. Baumann P, Nyman J, Hoyer M, et al: Outcome in a prospective phase II trial of medically inoperable stage I non–small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 27(20):3290–3296, 2009.
29. King CR, Freeman D, Kaplan I, et al: Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncology 109(2):217–221, 2013.
30. King CR, Collins S, Fuller D, et al: Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: Results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys 87(5):939–945, 2013.
35. Mahadevan A, Jain S, Goldstein M, et al: Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 78(3):735–742, 2010.
39. Bujold A, Massey C, Kim JJ, et al: Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 31(13):1631–1639, 2013.
41. Hellman S, Weichselbaum RR: Oligometastases. J Clin Oncol 13(1):8–10, 1995.
42. Salama JK, Milano MT: Radical irradiation of extracranial oligometastases. J Clin Oncol 2014. doi: 10.1200/JCO.2014.55.9567. in press.
43. Weichselbaum RR, Hellman S: Oligometastases revisited. Nature Rev Clin Oncol 8(6):378–382, 2011.
44. Gan GN, Weickhardt AJ, Scheier B, et al: Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. Int J Radiat Oncol Biol Phys 88(4):892–898, 2014.

REFERENCES

1. Hamilton AJ, Lulu BA, Fosmire H, et al: Preliminary clinical experience with linear accelerator-based spinal stereotactic radiosurgery. Neurosurgery 36:311–319, 1995.
2. Blomgren H, Lax I, Naslund I, et al: Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 34:861–870, 1995.
3. Uematsu M, Shioda A, Tahara K, et al: Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: A preliminary experience. Cancer 82:1062–1070, 1998.
4. Potters L, Kavanagh B, Galvin JM, et al: American society for therapeutic radiology and oncology (ASTRO) and American college of radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 76(2):326–332, 2010.
5. Benedict SH, Yenice KM, Followill D, et al: Stereotactic body radiation therapy: The report of AAPM task group 101. Med Phys 37(8):4078–4101, 2010.
6. Solberg TD, Balter JM, Benedict SH, et al: Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. Practical Rad Oncol 2(1):2–9, 2012.
7. Marks LB, Jackson M, Xie L, et al: The challenge of maximizing safety in radiation oncology. Practical Rad Oncol 1(1):2–14, 2011.
8. McCammon R, Schefter T, Gaspar L, et al: Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy (SBRT). Int J Radiat Oncol Biol Phys 73(1):112–118, 2009.
9. Olsen JR, Robinson CG, El Naqa I, et al: Dose–response for stereotactic body radiotherapy in early-stage non–small-cell lung cancer. Int J Radiat Oncol Biol Phys 81(4):e299–e303, 2011.
10. Rule W, Timmerman R, Tong L, et al: Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol 18(4):1081–1087, 2011.
11. Herfarth KK, Hof H, Bahner ML, et al: Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. Int J Radiat Oncol Biol Phys 57:444–451, 2003.
12. Olsen CC, Welsh J, Kavanagh BD, et al: Microscopic and macroscopic tumor and parenchymal effects of liver stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 73(5):1414–1424, 2009.
13. Stinauer MA, Diot Q, Westerly DC, et al: Fluorodeoxyglucose positron emission tomography response and normal tissue regeneration after stereotactic body radiation therapy to liver metastases. Int J Radiat Oncol Biol Phys 83(5):e613–e618, 2012.
14. Pan CC, Kavanagh BD, Dawson LA, et al: Radiation-associated liver injury. Int J Radiat Oncol Biol Phys 76(3):S94–S100, 2012.
15. Lee MT, Kim JJ, Dinniwell R, et al: Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 27(10):1585–1591, 2009.
16. Kavanagh BD, Schefter TE, Cardenes HR, et al: Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. Acta Oncol 45:848–855, 2006.
17. Palma DA, van, Sörnsen de Koste J, Verbakel WF, et al: Lung density changes after stereotactic radiotherapy: A quantitative analysis in 50 patients. Int J Radiat Oncol Biol Phys 81(4):974–978, 2012.
18. Timmerman R, Paulus R, Galvin J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303(11):1070–1076, 2010.
19. Stanic S, Paulus R, Timmerman RD, et al: No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early-stage peripheral non–small cell lung cancer: An analysis of RTOG 0236. Int J Radiat Oncol Biol Phys 88(5):1092–1099, 2014.
20. Chang JY, Liu H, Balter P, et al: Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non–small cell lung cancer. Radiat Oncol 7:152, 2012.
21. Timmerman R, McGarry R, Yiannoutsos C, et al: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 24(30):4833–4839, 2006.
22. Cox BW, Jackson A, Hunt M, et al: Esophageal toxicity from high-dose, single-fraction paraspinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 83(5):e661–e667, 2012.
23. Murphy JD, Christman-Skieller C, Kim J, et al: A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. Int J Radiat Oncol Biol Phys 78(5):1420–1426, 2012.
24. Kim DW, Cho LC, Straka C, et al: Predictors of rectal tolerance observed in a dose escalated phase I/II trial of SBRT for prostate cancer. Int J Radiat Oncol Biol Phys 89(3):509–517, 2014.
25. Wisnivesky JP, Bonomi M, Henschke C, et al: Radiation therapy for the treatment of unresected stage I-II non–small cell lung cancer. Chest 128(3):1461–1467, 2005.
26. Kaskowitz L, Graham MV, Emami B, et al: Radiation therapy alone for stage I non–small cell lung cancer. Int J Radiat Oncol Biol Phys 27(3):517–523, Oct 20 1993.
27. Sibley GS, Jamieson TA, Marks LB, et al: Radiotherapy alone for medically inoperable stage i non–small–cell lung cancer: The duke experience. Int J Radiat Oncol Biol Phys 40(1):149–154, 1998.
28. Baumann P, Nyman J, Hoyer M, et al: Outcome in a prospective phase II trial of medically inoperable stage I non–small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 27(20):3290–3296, 2009.
29. King CR, Freeman D, Kaplan I, et al: Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncology 109(2):217–221, 2013.
30. King CR, Collins S, Fuller D, et al: Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: Results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys 87(5):939–945, 2013.
31. Hodges JC, Lotan Y, Boike TP, et al: Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: An emerging initial radiation treatment option for organ-confined prostate cancer. J Oncol Pract 8(3 Suppl):e31s–37s, 2012.
32. Parthan A, Pruttivarasin N, Davies D, et al: Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. Front Oncol 2:81, 2012.
33. Hoyer M, Roed H, Sengelov L, et al: Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol 76(1):48–53, 2005.
34. Gurka MK, Collins SP, Slack R, et al: Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: A pilot trial demonstrating safety. Radiat Oncol 8:44, 2013.
35. Mahadevan A, Jain S, Goldstein M, et al: Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 78(3):735–742, 2010.
36. Tozzi A, Comito T, Alongi F, et al: SBRT in unresectable advanced pancreatic cancer: Preliminary results of a mono-institutional experience. Radiat Oncol 8(1):148, 2013.
37. Klein J, Dawson LA: Hepatocellular carcinoma radiation therapy: Review of evidence and future opportunities. Int J Radiat Oncol Biol Phys 87(1):22–32, 2013.
38. Andolino DL, Johnson CS, Maluccio M, et al: Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 81(4):e447–e453, 2011.
39. Bujold A, Massey C, Kim JJ, et al: Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 31(13):1631–1639, 2013.
40. Sanuki N, Takeda A, Oku Y, et al: Stereotactic body radiotherapy for small hepatocellular carcinoma: A retrospective outcome analysis in 185 patients. Acta Oncol (Madr) 53(3):399–404, 2014.
41. Hellman S, Weichselbaum RR: Oligometastases. J Clin Oncol 13(1):8–10, 1995.
42. Salama JK, Milano MT: Radical irradiation of extracranial oligometastases. J Clin Oncol 2014. doi: 10.1200/JCO.2014.55.9567. in press.
43. Weichselbaum RR, Hellman S: Oligometastases revisited. Nature Rev Clin Oncol 8(6):378–382, 2011.
44. Gan GN, Weickhardt AJ, Scheier B, et al: Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. Int J Radiat Oncol Biol Phys 88(4):892–898, 2014.