Chapter 8
Stereotactic Body Radiation Therapy (SBRT) or Alternative Fractionation Schedules

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Abstract The use of hypofractionated regimens for the treatment of tumors with radiation has come full circle. After the discovery of X-rays and their utilization for cancer treatment, the initial fractionation schemes were primarily hypofractionated in nature. However, due to technical limitations and associated toxicities, more protracted fractionated regimens eventually became the foundation for modern radiation therapy. With the advance of imaging and radiation delivery systems, interest in more hypofractionated approaches was revived. Stereotactic ablative radiation therapy (SABR; also referred as stereotactic body radiation therapy, SBRT) is the most abbreviated form of hypofractionation, typically utilizing 1–5 fractions for treatment. Its strengths include high rates of tumor control via a convenient, noninvasive outpatient procedure. Toxicities related to high, ablative radiation doses still are a potential concern; however, recent clinical trials for a variety of tumor sites have shown good outcomes in properly selected patients. This chapter will discuss the potential for SBRT/SABR to improve the therapeutic response. The use of SBRT/SABR regimens to treat lesions within the lung, liver, spine, and prostate will be reviewed. Due to more mature data in regard to the safety and efficacy, cost-effectiveness of the treatment, and potential for immunomodulatory effects, SBRT/SABR has become more wildly utilized in cancer treatment.

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Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Ablative Body Radiosurgery (SABR)

Introduction

After the discovery of X-rays in 1895 and radioactivity in 1896, initial radiation cancer treatments were mostly hypofractionated. Treatments were limited in giving higher doses to the skin and superficial structures than to a deeper tumor target. Quality assurance measures were lacking to ensure accurate dose deposition. These approaches lead to tumor responses, however, with significant late tissue effects. Despite these limitations, hypofractionation remained the primary treatment schedule due to patient convenience and technical considerations with treatment delivery.

Early radiotherapy pioneers, including Friedrich Dessauer, identified the problems with the state of technology for delivering hypofractionated treatments. In 1905, Dessauer proposed that improvements could be achieved with the application of homogeneous dose to the tissue and eventually leading to the formulation of ideas of multibeam or multisource irradiation [1].

At the same time, Claudius Regaud was performing his seminal experiments relating to the irradiation of the testis. He observed that cells undergoing mitosis were more sensitive to radiation, whereas the more differentiated cells were less sensitive [2]. This work led to the "Law of Bergonie and Tribondeau" stating that the effects of irradiation on cells are more intense the greater their reproductive activity, the longer their mitotic phases, and the less differentiated, forming the biological basis for fractionation [3].

In 1932, Henri Coutard presented his groundbreaking findings at the American Congress of Roentgenology demonstrating that protracted fractionated radiotherapy had cured deep tumors with significantly less toxicity previously seen [4]. Afterward, radiation oncologists across the world mostly abandoned hypofractionated as a method for curative treatment. Interestingly, Coutard believed in both approaches stating that choice of fractionation should depend on the initial volume of the target (small targets warrant hypofractionation, whereas large should be more protracted) [5].

It took until the 1950s when Lars Leksell broke from the perceived rationale of conventionally fractionated radiotherapy (CFRT) by using large-dose single sessions of radiation delivery in the central nervous system [6]. Although a single large-dose radiation treatment was historically prohibitive, Leksell's approach defied conventional wisdom by its technology and administration. Unlike CFRT, which often irradiates much larger volumes of normal tissue to the prescription dose than the tumor itself, Leksell's stereotactic radiosurgery (SRS) went to great lengths

to avoid delivering high dose to nontargeted normal tissues. Whatever normal tissue was included, either by being adjacent to the target or by inferior dosimetry, was likely damaged. However, if this damaged tissue was small in volume or noneloquent, the patient did not suffer clinically apparent toxicity, even as a late event.

Building upon these results, Lax and Blomgren at the Karolinska Institutet in Sweden separated from the established traditions of CFRT and began to explore the use of alternative hypofractionated radiation treatment regimens for lung, liver, and selected other malignant extracranial tumors. They constructed a stereotactic body frame that would simultaneously enable comfortable and reliable immobilization and dampening of respiratory motion treating patients with extracranial, localized tumors with ablative doses of radiation that ranged from 7.7 to 45 Gy in 1–4 fractions [7]. At the same time in Japan, Uematsu and colleagues developed technologies to deliver stereotactic radiation to lung tumors [8]. Initially the treatments were called extracranial stereotactic radioablation and later stereotactic body radiation therapy (SBRT) [9, 10]. More recently, the descriptive term stereotactic ablative radiotherapy (SABR) has been used [11].

Defining characteristics of SBRT/SABR include the following [12]: (1) secure immobilization avoiding patient movement for the typical long treatment sessions; (2) accurate repositioning from simulation to treatment; (3) minimization of normal tissue exposure attained by using multiple (e.g., 10 or more) or large-angle arcing small aperture fields; (4) rigorous accounting of organ motion; (5) stereotactic registration (i.e., via fiducial markers or surrogates) of tumor targets and normal tissue avoidance structures to the treatment delivery machine; and (6) ablative dose fractionation delivered to the patient with subcentimeter accuracy.

Radiobiological Modeling of SBRT/SABR

Classical understanding of the mechanisms of radiation-induced tumor cell killing centers on the hypothesis that DNA is the main target of ionizing radiation, leading to single- and double-strand breaks. Different mathematical models have been developed to compare tumor control and normal tissue toxicity profiles for various radiation schedules and fraction sizes. Since the development of the linear-quadratic (LQ) formalism by Lea and Catcheside to describe the relationship between radiation dose and the incidence of chromosomal translocations, it has served as the primary basis for modeling radiation dose effects [13]. The LQ model describes cell killing as a single-hit versus double-hit hypothesis, where the linear cell kill is expressed by the α component, while the quadratic cell kill is expressed by the β component [14]. The α/β ratio is obtained from isoeffect curves using the survival fractions of a cell line at different doses per fraction [15]. This ratio is primarily utilized to predict the clinical effects in response to changes in fraction size. With regard to tumors, a high α/β ratio predicts higher sensitivity to CFRT, while a lower α/β ratio predicts lower sensitivity to CFRT. Most tumors typically possess a high α/β ratio (approximately 8–10) relative to most normal tissues, which demonstrate lower α/β ratios (approximately 1–4).

Not all hypofractionated radiotherapy is ablative. In general, ablation occurs at dose levels that correspond to the exponential (linear region on a logarithmic scale) portion of the cell survival curve, which would generally involve daily dose levels of >8 Gy. Below this dose range, cells have more capacity to repair. The logarithm of cell survival as a function of dose in the lower-dose region exhibits a curviness called the shoulder. More conventional and nonablative hypofractionated radiotherapy is delivered on the shoulder. The range of 2.25–8 Gy per fraction, still considered hypofractionated, has mostly been used for palliation of metastatic disease. More recently, though, investigators treating common diseases like breast and prostate cancer have used nonablative hypofractionation in patients with curable tumors. This was partly for the cost savings associated with fewer overall fractions, but in some cases, such hypofractionation has a biological rationale for improving the therapeutic ratio.

Based on experimental and clinical data, the LQ model seems to predict biological effective dose (BED) accurately for fraction sizes less than 3.25 Gy [16]. Due to the fact that typical doses for SBRT/SABR fall outside of this range, the LQ model breaks down as does not accurately predict the BED for extremely hypofractionated regimens [16–19]. The development of more accurate models to predict the responses of tumors to hypofractionated radiotherapy has been attempted. The universal survival curve, modified linear-quadratic model (LQL), and the generalized linear-quadratic model all have shown better radiobiological modeling of high dose per fraction than the LQ model, with moderate success at maintaining accuracy within the conventionally fractionated range [16, 18, 20]. In an attempt to address this discrepancy, a universal survival curve was constructed which hybridized the LQ model and the multitarget model [20]. The multitarget model better describes the survival curve for ablative doses beyond the shoulder or the transition dose D_T. These models primarily predict the tumor control to hypofractionated radiotherapy; however, better estimation of normal tissue toxicity with larger doses per fraction is required.

Limitations to predict clinically relevant endpoints exist in simple radiobiological modeling due to the presence of additional factors, including dose rate, period of time over which treatment is delivered, tissue type irradiated, and competing cell death mechanisms besides DNA damage. These may include immunological activation mediated by the release of antigens, damage to cell membranes and organelles, and additional mechanisms related to ablative therapy [21].

Several groups have described tissues and their radiation response according to the organization of the smallest functional subunit [22, 23]. Structurally defined tissues can only repair radiation damage by recruiting their own stem cells and have a lower radiation tolerance per functional subunit. Generally, organs comprised of such structurally defined subunits, also called parallel functioning tissues, and are large organs like the peripheral lung and liver. Parallel organs display significant redundancy in the number of subunits performing the same function to overcome the poor tolerance to damage. In contrast, tissues made up predominately of structurally undefined subunits are much more tolerant of radiation damage per subunit

because of their ability to recruit clonogenic cells from neighboring tissues for repair. Organs made up of structurally undefined subunits like the esophagus, major ducts and airways, and spinal cord are referred as serially functioning tissues and perform critical functions acting as a conduit. Despite possessing a higher radiation tolerance, if a section of a serially functioning tissue is damage anywhere along its length, all downstream function may be effected [12]. The potential to elicit such tissue injury when utilizing ablative doses is a major consideration needed to be taken into account when developing treatment plans.

The underpinning of radiobiological understanding of radiation therapy is based on the differences of chromosomal damage within tumor versus normal cells resulting from the relatively homogenous dose exposures of CFRT. It could then be expected that the large dose per fraction associated with SBRT/SABR would cause tremendous DNA damage within any tissue exposed to this dose. Therefore as mentioned above, it is critical to geometrically partition the dose levels received by the tumor and normal tissues. Additionally, SBRT/SABR dose distributions are typically engineered to be heterogeneous, allowing large variations of dose between tumor, adjacent normal tissue, and more removed normal tissues. Due to this dose variability, comparisons between SBRT/SABR and CFRT can become complicated [24].

Immunological Effects of Ablative Radiation

In addition to the DNA damage effects described above, a high intratumoral dose achieved with SBRT/SABR might optimize antitumor mechanisms by stimulating local and direct immune responses in the local microenvironment and antigen-presenting cells (APCs) [25]. High-dose-per-fraction radiation (>8 Gy per treatment fraction) may also generate stromal effects that are not accounted for in traditional radiobiological modeling [26, 27]. It has been suggested that higher doses per fraction result in increased tumor endothelial apoptosis and vascular damage, a phenomenon seen only in high-dose-per-fraction treatment schedules, may contribute significantly to cell kill [26, 28]. Relatively radiation-insensitive tumor stem cells may also compromise the ability of low-dose fractions to achieve durable tumor control; it has been hypothesized that higher doses per fraction can overcome these cells' ability to repair sublethal damage [29]. Higher doses per fraction, as opposed to conventional 2 Gy doses, can also prime T cells in lymphatic tissue, leading to more significant CD8+ T-cell-dependent eradication of disease, as well as the induction and expression of effector cytokines and other inflammatory mediators [30]. Such a pro-inflammatory environment laden with cytokine production can increase permeability of local vasculature and stimulate APCs to mature more effectively. More recently, increased interest in the potential ability of SBRT/SABR to promote an abscopal response in conjunction with immunomodulatory agents has been investigated. Two case reports of combination SBRT/SABR and ipilimumab (anti-CTLA-4) have shown abscopal effects in metastatic melanoma and non-small cell lung cancer [31, 32]. A Phase I trial of SBRT/SABR and high-dose interleukin-2 for

patients with metastatic melanoma or renal cell carcinoma revealed abscopal responses in several patients [33]. The combination of greater degree and/or different modes of DNA damage as well as injury to the tumor microenvironment arising from the use of hypofractionated or single-fraction radiation therapy may work synergistically to cause irreparable and lethal injuries to the irradiated cells [28, 34, 35].

SBRT/SABR for Primary Management of NSCLC

Lung cancer is the second most diagnosed cancer and the leading cause of cancer-related mortality in the United States [36]. Of patients newly diagnosed with non-small cell lung cancer (NSCLC), 15–20 % are found to have stage I disease [37]. Surgical resection is the treatment of choice for these patients. However, up to 30 % are deemed inoperable because of comorbidities [38]. SBRT/SABR has proven efficacy in the treatment of patients with early-stage, medically inoperable NSCLC [39, 40] with an emerging indication in the setting of limited metastatic disease [41–52].

For patients with medically inoperable NSCLC, dose escalation using conventional fractionation was initially explored to improve the probability of local control. Radiation Therapy Oncology Group (RTOG) Protocol 7301 investigated multiple dosing regimens for patients with T1-3 N0-2 disease, including 40 Gy delivered in a split regimen of two courses of 20 Gy delivered in 5 fractions (40 Gy total in 10 fractions) with a 2-week break between courses, and continuous regiments escalating the dose from 40 to 60 Gy. The failure rate within the irradiated volume was 48 % in the 40 Gy continuous regimen, 38 % for the 40 Gy split course and 50 Gy regimen, and 27 % in the 60 Gy continuous regimen [53]. RTOG Protocol 9311 then escalated doses from 65 to 90.3 Gy using 3D conformal radiation therapy in inoperable patients and found that treatment could safely be delivered in daily fraction sizes of 2.15 Gy to a total dose of 77.4 Gy or 83.8 Gy provided that the volume of the lung receiving 20 Gy could be constrained to less than 25 % of the total lung volume. The study attained locoregional control rates at 2 years of 55–78 % at the MTD [54].

A later dose-escalation study conducted by Rosenzweig et al. treated patients with inoperable NSCLC using 3D conformal radiation therapy, with fraction sizes of 1.8 Gy for doses ≤81 Gy and 2 Gy for doses >81 Gy. Dose-escalation levels included 70.2, 75.6, 81.0, 84.0, and 90 Gy; unacceptable pulmonary toxicity occurred at 90 Gy, and the maximum tolerated dose (MTD) was established at 84 Gy [55]. Long-term results of this study were reported by Sura et al. and included 55 patients with stage I/II disease. They demonstrated that treating the primary lesion with escalated doses >80 Gy in 2 Gy fractions resulted in 5-year local control (LC) and overall survival (OS) outcomes of 67 % and 36 %, respectively [56].

In order to continue to improve LC and OS in this patient population, protocols have sought to improve the therapeutic ratio with the addition of chemotherapy or by changing the dose per fraction. Researchers at Indiana University reported a

Phase I study in which patients with T1–T2 N0 NSCLC were treated with escalating doses of SBRT/SABR, starting at 24 Gy in 3 fractions and increasing to 60 Gy (for T1 lesions) or 72 Gy (for T2 lesions) in 3 fractions to determine the maximum tolerated dose (MTD). The MTD was not reached for T1 lesions at 60 Gy, and for T2 lesions an MTD of 66 Gy was established based on bronchitis, pericardial effusion, hypoxia, and pneumonitis. Crude rates of local failure were 21 % in both the T1 and T2 cohorts, and a dose response was noted with only one local failure observed with fraction sizes of >16 Gy per fraction [10, 39]. These doses were calculated without correction for tissue inhomogeneity; subsequent doses used inhomogeneity correction and as a result appear slightly lower.

A subsequent Phase II multicenter trial (RTOG 0236) further evaluated the toxicity and efficacy of stereotactic body radiation therapy in a high-risk population of patients with T1-2aN0 (lesions <5 cm in size) early-stage, medically inoperable NSCLC. Doses of 54 Gy in 3 fractions were delivered, and an estimated 3-year local control rate of 97.6 % was observed, with an overall survival rate of 55.8 % at 3 years [40]. Based on this study, stereotactic body radiotherapy (SBRT) is now the standard of care for medically inoperable early-stage non-small cell lung cancer (NSCLC) or those patients who refuse surgery. Further work is being done to optimize dose delivery for early-stage NSCLC; the RTOG conducted RTOG Protocol 0915, a randomized Phase II study that compared two different SBRT/SABR treatment schedules for medically inoperable patients with stage I peripheral NSCLC, in which patients were randomized to receive 34 Gy in a single fraction or 48 Gy in four daily consecutive fractions of 12 Gy per fraction. This protocol is now closed to accrual, and final results are pending; preliminary data suggest that 34 Gy may be more efficacious with respect to local control and equivalent in toxicity profile, and a comparison of 34 Gy in one fraction to 54 Gy in 3 fractions is planned.

Continued evaluation of dose response outside of trials has been performed. In a review of the National Cancer Data Base (NCDB), 498 patients were identified and evaluated for response to SBRT/SABR. These patients were treated with a range of dosing regimens, with the most common being 60 Gy in 3 fractions, 48 Gy in 4 fractions, 54 Gy in 3 fractions, 45 Gy in 3 fractions, and 48 Gy in 3 fractions. Outcomes were evaluated with respect to biologically effective dose (BED) [57], which is calculated according to the simplified formula:

$$\mathrm{BED} = nd\left(1 + d/\left(\alpha/\beta\right)\right)$$

where n = number of treatment fractions, d = dose per fraction, and α/β is the ratio of the linear and quadratic components of the cell survival curve; for the purposes of their study, an α/β ratio of 10 was assumed. For example, a regimen of 54 Gy in 3 fractions would have a BED of $18 \times 3 \times \left(1 + 18/10\right)$ or 151.2. They found that increasing BED to doses >150 Gy equivalent was associated with improved survival in patients undergoing SBRT/SABR for larger (T2) tumors [58].

While local control rates with SBRT/SABR in early-stage NSCLC are excellent [40, 59], distant failure is common, occurring in 20–30 % of patients in 3–5 years [40, 60–62]. Future efforts in the treatment of early-stage NSCLC will naturally

include optimization of treatment delivery to safely and accurately deliver ablative doses to tumor while limiting normal tissue toxicity, but it is likely that incorporation of appropriately timed and administered cytotoxic, targeted, and immunotherapy-based treatments will be required to optimize outcomes in terms of out-of-field tumor recurrence and overall patient survival after SBRT/SABR.

Specific Issues Associated with SBRT/SABR for Targets in the Lung

Escalating the dose to the target in the lung has been shown to be effective in terms of killing the tumor cells, but the normal nearby tissues must be taken into account; tumor control does come at a price. The lung may be considered both a parallel and serial organ, in that there is some redundancy due to its paired nature and parenchymal reserve, but injury to a central structure may impair function of a large downstream volume; one aspect of this is the proximal bronchial tree. Ablative doses given to a very proximal branch of the airway could cause injury that impairs downstream function and lead to significant patient pulmonary toxicity; additionally, large vessels run in close approximation to these large branches and could also potentially be a target for injury. In a study by Timmerman et al., building on an earlier dose-escalation study [10], 70 patients with T1-2 N0 medical inoperable NSCLC were treated with either 60 Gy in 3 fractions (for T1 disease) or 66 Gy in 3 fractions (for T2 disease); these doses were also calculated without correction for tissue inhomogeneity, and there was no restriction on tumor location. Local tumor control remained very high, 95 % at 2 years; however, on follow-up, eight patients had serious grade 3 or 4 toxicities (declining pulmonary function, pneumonia, effusion, apnea), and six patients died of possible grade 5 toxicities, including one fatal hemoptysis four infectious pneumonias, and one pericardial effusion. Tumor location was associated with severe toxicity, and this study identified that dose delivery to targets overlapping the proximal bronchial tree with a 2 cm expansion (consisting of the carina, the right and left main bronchi, the right and left upper lobe bronchi, the bronchus intermedius, the right middle lobe bronchus the lingular bronchus;, and the right and left lower lobe bronchi) was most predictive of serious adverse effects. This area was defined as a "no-fly zone" for SBRT/SABR in the lung of very high fraction sizes (>10 Gy per fraction) [63].

Effective dose delivery for patients with "central tumors" is an area of active investigation. The RTOG recently closed RTOG Protocol 0813, which was a Phase I/II study of SBRT/SABR for the treatment of early-stage, centrally located NSCLC in medically inoperable patients. They defined central tumors as those with any overlap with a 2 cm expansion from the previously defined proximal bronchial tree, as well as any lesions adjacent to the mediastinal or pericardial pleura. Dose was delivered in 5 fractions every other day, starting at 50 Gy in 5 fractions and escalating to 60 Gy in 5 fractions.

SBRT/SABR for Metastases to the Spine

Radiation therapy has a role in the management of both primary and metastatic lesions of the spine, although the vast preponderance of metastatic disease has led to more extensive research and clinical evaluation of treatment techniques. Metastatic disease in the spine is common, accounting for up to 70 % of all metastases to the bone and affecting up to 10 % of all cancer patients [35, 64]. Spine involvement can result in back pain (the most common presenting symptom) and deterioration in functional status and quality of life [65]. Compression or invasion of the spinal cord, cauda equina, or exiting nerve roots can lead to disabling or even life-threatening neurological symptoms [66].

Conventionally fractionated radiation therapy for spine metastases is generally a palliative therapy and may not be sufficient alone to restore and maintain neurological function; in a study by Patchell et al., patients with epidural spinal cord compression were randomized to conventional external beam radiation therapy (30 Gy in 10 fractions) alone or direct decompressive surgery followed by radiation therapy. Patients who underwent combined modality treatment had significantly improved neurological outcomes, with more patients able to ambulate after treatment (84 % vs 57 %, $P=0.001$) and longer sustained ambulatory status (122 days vs 13 days, $P=0.003$). A small survival benefit was also noted (126 days vs 100 days, $P=0.033$) [67]. Conventional external beam therapy has been shown to achieve local control rates range less than 50 % [68–71]. Even in the postoperative setting, in a large retrospective study by Klekamp and Samii, patients receiving low-dose conventional external beam radiation therapy following surgery for spinal lesions had documented local failure as high as 58 % at 6 months, and these local failures led to neurologic deterioration in 69 % of the patients within 1 year and in 96 % of patients within 4 years [69].

Multiple studies support the hypothesis that dose escalation, particularly in terms of dose per fraction, improves the likelihood of local control in lesions metastatic to the spine [72–75]. Hartsell et al. conducted a randomized trial in which 898 patients with painful bone lesions (patients with spinal cord or cauda equina compression were excluded) were treated with either 8 Gy in 1 fraction or 30 Gy in 10 fractions. The two regimens were equivalent in terms of pain and narcotic relief at 3 months, with less acute grade 2–4 toxicity in the 8 Gy arm (10 % vs 17 %); retreatment rates were doubled in the 8 Gy arm (18 % vs 9 %), suggesting that a single high-dose fraction could provide comparable benefit to a more protracted course [76]. With advances in radiation therapy delivery, fraction sizes above 8 Gy could be delivered to spinal targets while constraining dose to the spinal cord and/or cauda equina [77]. The use of SBRT/SABR techniques with precise target delineation allows for safe delivery of radiation while limiting dose to the nearby spinal cord; techniques for defining the spinal cord vary, with some institutions preferring a CT-myelogram-defined cord immediately prior to simulation [78, 79], while other institutions define the cord on the basis of a registered and fused T1- and T2-weighted MRI, which is the method used in the current RTOG (now NRG Oncology) 0631 protocol.

A more conservative approach pursued at some institutions defines the organ at risk as the entire thecal sac or canal [80]; this approach is often used at the level of the cauda equina [74].

A Phase I/II non-dose-escalating study was performed by Chang et al. using SBRT/SABR for spinal metastasis, pattern of failure analysis. In their initial Phase I report [81], they treated 15 patients with SBRT/SABR to a goal dose of 30 Gy in 5 fractions, constraining the spinal cord to a maximum dose of 10 Gy. Five of the patients treated on the study had been previously irradiated. No neurotoxicity or grade 3–4 toxicities were observed. In the subsequent failure analysis report [82], a total of 63 patients with 74 tumors had been treated to doses of 30 Gy in 5 fractions or 27 Gy in 3 fractions; 1-year freedom from tumor progression was 84 %. Of the local recurrences, 47 % were located in the epidural space, where effective dose delivery was most constrained by the proximity of the spinal cord [81, 82]. The correlation between failure to deliver maximal dose and increased risk of failure has received attention from multiple investigators. Lovelock et al. [83] reported a study of dosimetric coverage of target lesions and found that portions of gross tumor volumes (GTV) receiving less than 15 Gy were at highest risk of failure. These deficits in GTV dosimetry were often due to constraints placed on the radiation treatment planning process in terms of the maximum dose (D_{max}) permitted to the spinal cord.

A dose-escalation protocol initiated at Memorial Sloan Kettering Cancer Center (MSKCC) using image-guided single-fraction high-dose radiotherapy for metastatic disease established 24 Gy to the planning target volume (PTV) as an effective dose to achieve 85–95 % tumor control for spine lesions, osseous metastases, and soft-tissue/lymph node metastatic deposits (MSKCC Protocol 06-101) [77, 84]. Yamada et al. reported on 93 patients with 103 spinal metastases treated with 18–24 Gy in a single fraction. Using this regimen, 90 % overall actuarial local control was achieved at a median follow-up of 15 months; patients treated with the highest dose level of 24 Gy had superior local control (95 % vs 80 % for single-fraction treatments <24 Gy) [77].

Some tumors, such as renal carcinoma and sarcoma, have been shown to be less sensitive to fractionated radiation than other histologies and also have limited systemic treatment options. These tumor histologies provide a particularly useful model for testing the efficacy of SBRT/SABR, as local control outcomes are not confounded by competing therapies [85]. Zelefsky et al. reported on tumor control outcomes after hypofractionated and single-dose SBRT/SABR for extracranial metastases from renal cell carcinoma; of the 105 lesions treated on the study, 59 (56 %) were located in the spine. For patients who received 24 Gy in a single fraction, 3-year local progression free survival was 88 %; for patients receiving single fractions of less than 24 Gy or hypofractionated regimens of 24–30 Gy in 3–5 fractions, 3-year local progression free survival was 21 % and 17 %, respectively [75]. Folkert et al. reported on 88 patients with 120 discrete metastases from high-grade sarcoma to the spine, treated with hypofractionated or single-fraction SBRT/SABR. Local control at 12 months was 88 %, with single-fraction treatments of 24 Gy having superior outcomes (1-year local control of 91 %, compared to 84 % for hypofractionated courses of 24–26 Gy in 3–6 fractions) [73].

A currently open RTOG trial, RTOG 0631 (NCI designation NCT00922974), is comparing the relative benefit of 2 single-fraction regimens: 8 Gy in 1 fraction delivered with conventional techniques and 16–18 Gy delivered in 1 fraction using SBRT/SABR techniques. Clinical response, in terms of pain reduction at 3 months, is the primary objective of the Phase III portion of the study. Initial Phase II results have been published demonstrating the feasibility and reproducibility of the technique [86]; while local control outcomes are not a specific objective of the study, the potential exists to provide a direct comparison of objective radiographic response to low- and high-dose single-fraction regimens.

Specific Issues Associated with SBRT/SABR for Targets in the Spine

Treatment of targets in the spine can be particularly complex as the spine circumferentially encloses critical neural structures. A critical toxicity that must be taken into account with treatments affecting the spinal cord is radiation myelitis. Radiation myelopathy is defined as clinical signs and/or symptoms of sensory or motor deficits, with progressive loss of function or neuropathic pain, referable to a level of the spinal cord treated by radiation therapy and confirmed by radiographic means [87–89].

The generally accepted dose limit for the spinal cord is 45 Gy at 1.8–2.0 Gy/fraction [89]; 50 Gy is observed in otherwise healthy patients treated with curative intent where the tumor location prohibits limiting the cord to a lower dose, with an attendant 5 % risk of myelopathy at 5 years [87, 89]. For patients undergoing high-dose spinal cord radiosurgical procedures, spinal cord tolerance is defined as a cord maximal dose of 14 Gy or less than 10 Gy to 10 % volume of the spinal cord per level [77, 90]. In the event of failure, these limitations may preclude or impair the ability of radiation oncologists to offer effective salvage therapy with external beam techniques. Toxicity resulting from repeat irradiation is a subject of open investigation, with thresholds of 100–135 Gy in biologically effective dose (BED) proposed for late complications due to repeat irradiation of the spinal cord [91–93]. Outcomes were evaluated with respect to biologically effective dose (BED) [57], which is calculated according to the simplified formula:

$$\mathrm{BED} = nd\left(1 + d/\left(\alpha/\beta\right)\right)$$

where n = number of treatment fractions, d = dose per fraction, and α/β is the ratio of the linear and quadratic components of the cell survival curve; for the purposes of spine irradiation, an α/β ratio of 2 may be assumed. For example, a tolerance dose of 14 Gy in 1 fraction would have a BED of $14 * 1 * \left(1 + 14/2\right)$ or 112 Gy.

Preclinical data exists in swine models, as well as several published institutional experiences with multiply irradiated patients, that suggests that the tolerance of the human spinal cord to re-irradiation may be greater than currently assumed and

practiced. A study by Medin et al. [94] used a swine model in which two sets of pigs underwent single-fraction SRS at a series of increasing spinal cord D_{max} (approximately 15, 17, 19, 21, 23, and 25 Gy); one set had previously undergone irradiation of the spinal cord 1 year prior to SBRT/SABR, receiving 30 Gy in 10 fractions (BED = 75 Gy). No differences in the rates of spinal cord injury were noted in the previously irradiated swine cohort compared to the unirradiated cohort, and no neurologic injuries were noted at spinal cord D_{max} <18.8 Gy. In humans, Katsoulakis et al. [95] studied a cohort of ten patients treated with three courses of radiation to the same site in the spine; the median spinal cord total D_{max} BED for the cohort was 141.5 Gy BED (range 103.8–203.4 Gy BED). In this cohort, no cases of clinical radiation myelopathy were observed with a median total follow-up of 40 months from the first course of radiation and 12 months from the third course of radiation. Additionally, no MRI spinal cord signal changes were noted.

Determining the re-irradiation tolerance of the spinal cord is the objective of a prospective Phase I clinical trial investigating the use of single-fraction re-irradiation following local progression of mobile spine and sacral lesions that have previously received radiation therapy. Patients on this trial will be treated with single-fraction SBRT/SABR at three cord tolerance levels, starting with a spinal cord/cauda D_{max} of 14 Gy, escalating to 16 and then 18 Gy (NCI designation NCT02278744).

SBRT/SABR for Primary Liver Cancer

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of cancer death [96]. Hepatocellular carcinoma most commonly arises within a background of chronic liver disease [97], and the most common risk factors for the development of HCC are alcohol use and viral infection with hepatitis B and/or hepatitis C [98]. In the United States, the incidence will continue to rise dramatically necessitating early diagnosis and definitive therapy [99]. Due to the increasing incidence of HCC, routine surveillance strategies are in place which allow for earlier detection of disease in patients at high risk [100].

The current treatment schema for patients with HCC is defined by the Barcelona Clinic Liver Cancer (BCLC) strategy. This takes into account the quantity of tumors, the size of tumors, Child-Pugh's score, and extent of invasion [101]. Potentially curative treatment for patients with HCC can be performed with orthotopic liver transplantation (OLT), which treats both the underlying cirrhosis as well as the malignancy. Candidacy for liver transplantation is based on patients with early-stage disease, consisting of Child-Pugh score A–B, a single nodule <5 cm or 3 nodules <3 cm, and candidacy for transplantation.

Aside from OLT, surgical resection and percutaneous ablation are the treatments which provided the highest potential of cure [100]. Percutaneous radiofrequency ablation is the treatment of choice for patients not candidates for surgical resection. During treatment, the tumor and a margin of adjacent hepatic tissue are treated with

results as effective as resection for small, solitary nodules of HCC [102]. Transarterial chemoembolization is a procedure which takes advantage of the dual blood supply of the liver to deliver antineoplastics plus a gelatin sponge to arterial vasculature supplying the tumor [103]. The seminal meta-analysis of TACE versus systemic therapy found an improvement in the 2-year survival rate [104], and it is recommended for patients with BCLC intermediate-stage disease.

For patients with BCLC early-stage disease, SBRT/SABR can be considered as an alternative for patients not amenable to RFA due to tumor size or proximity to vessels. A substantial proportion of patients present with disease outside of transplant criteria or will progress outside of transplant criteria while on the waiting list, which necessitates the need for "bridging" therapies. It is here where modalities for downstaging or bridging can be aided by the utilization of SBRT/SABR. Furthermore, among patients with BCLC intermediate-stage disease, SBRT/SABR can be used following failure of TACE or as an alternative for TACE in patients who are not candidates for therapy. Follow-up of patients treated with SBRT/SABR with HCC includes dedicated liver imaging, ideally with MRI. There is considerable work being performed on characterizing imaging features in the cirrhotic liver post-SBRT/SABR, with Fig. 8.1 showing features of a treated lesion.

Our commonly utilized dose regimen for patients with HCC is based on the Indiana University experience. In a Phase I feasibility trial, patients with HCC were treated with dose escalation from 36 Gy in 3 fractions to a total dose of 48 Gy in 3 fractions if dose-limiting toxicities were not suffered [105]. Patients were eligible for this trial if they had Child-Pugh score A or B, a solitary tumor less than 6 cm in size or three lesions with total diameter less than 6 cm, and adequate liver function. In this trial, patients were treated in the Elekta Stereotactic Body Frame with abdominal compression to minimize diaphragmatic motion to less than 0.5 cm.

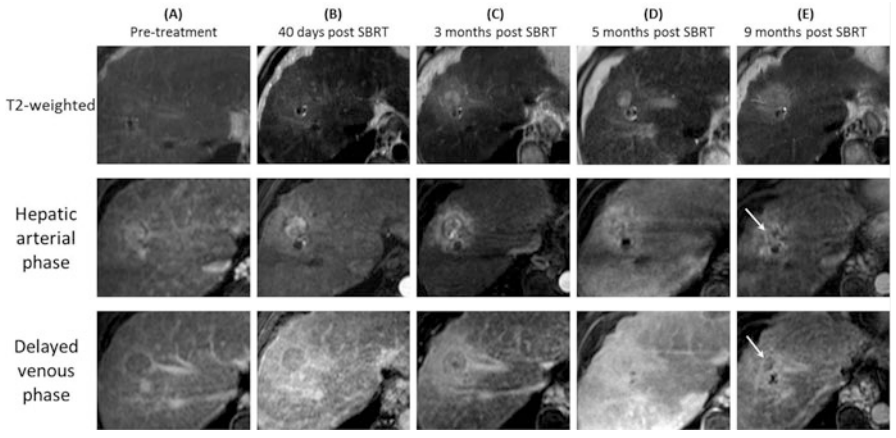

Fig. 8.1 HCC treated with SBRT. Pathognomonic arterial enhancement and venous washout seen pretreatment, which gradually resolved representing tumor response. T2-weighted imaging shows progressive evolution of edema within irradiated volume (**a**–**e**) [145]

Patients had daily image guidance with cone-beam CT scans prior to the delivery of each fraction. The target volume was delineated based on CT-based imaging, with no clinical target volume expansion and a minimum of 5 mm axial and 10 mm craniocaudal planning target volume expansion. Patients with portal vein thrombosis were allowed on the protocol, and the entire length of the thrombus was treated with a 1 cm margin. Key normal tissue constraints were that 1/3 of the uninvolved liver received less than or equal to 10 Gy for Child-Pugh class A patients and that 1/3 of the uninvolved liver received less than or equal to 15 Gy for Child-Pugh class B patients. Renal constraints included less than 2/3 of the right kidney receiving greater than 15 Gy and 1/3 of the left kidney receiving greater than 15 Gy. The maximum bowel and stomach dose were 12 Gy. In this study, the dose was successfully escalated to patients with Child-Pugh class A to 48 Gy in 3 fractions without reaching dose-limiting toxicity. However, in patients with Child-Pugh class B cirrhosis, the maximum tolerated dose was 40 Gy in 5 fractions due to two patients suffering grade 3 liver toxicity. With long-term follow-up, the Indiana experience found positive rates of 2-year local control of 90 % among the treated population. There were no long-term grade 3 or higher non-hematologic toxicities, and 20 % of patients were found to experience progression in the Child-Pugh score at 3 months [106].

A second key Phase I/II trial was performed by Princess Margaret University and the University of Toronto [107]. In this trial, patients with Child-Pugh score A with no more than five liver tumors with a maximal dimension of 15 cm were enrolled. Patients in this trial were treated to a dose of 30–54 Gy in six fractions, with the maximum effective irradiated liver volume of 60 %. No patients in this trial suffered classic RILD or dose-limiting toxicity, with a decline in Child-Pugh score at 3 months occurring in 29 % of the cohort. Like the Indiana experience, the local tumor control was excellent at 87 % at 1 year. These two trials provide data for the efficacy for SBRT in the setting of well-controlled and designed clinical trials.

While these studies were limited to patients with preserved to mildly elevated liver function, there is evidence for the treatment of patients with Child-Pugh B7 or B8 with SBRT/SABR as well. The Princess Margaret group performed a prospective study with patients with Child-Pugh B7 or 8 with less than 10 cm of HCC tumor [108]. Patients received a median dose of 30 Gy in 5 fractions; however, as expected with their more fragile liver function, 63 % of the cohort had a decline in their Child-Pugh score at 3 months. Sorafenib is a tyrosine kinase inhibitor which is used in patients with advanced HCC, showing an improvement in overall survival compared to placebo. Currently an RTOG trial (RTOG 1112) is enrolling patients with advanced-stage HCC to daily sorafenib versus SBRT/SABR alone followed by daily sorafenib. The primary endpoint of the trial is overall survival with secondary endpoints evaluating the safety profile of SBRT/SABR plus sorafenib. This trial will potentially further expand the utilization of SBRT/SABR patients with advanced HCC.

SBRT/SABR for the Treatment of Liver Metastases

Because of its rich blood supply, hematogenous metastases to the liver are common among patients with solid organ malignancies [109]. Colorectal cancers are the most common primary malignancy to metastasize to the liver due to drainage via the portal circulation, with up to 50 % of patients suffering hepatic metastases within 5 years [110]. A subset of patients with metastatic disease present with oligometastases, a hypothesis popularized in 1995 by Hellman and Weichselbaum. It states that metastatic disease occurs in a stepwise manner, with limited metastases initially followed by progression to widespread disease [111]. Early in the spectrum, metastases may be limited in number and location [112]. Improvements in imaging including PET/CT and MRI have allowed for identification of isolated metastatic deposits with higher sensitivity and specificity than ever before. A significantly greater proportion of patients may be identified early in the metastatic spectrum and offered potentially curative local treatment with liver metastases.

Treatment of oligometastases was first performed via surgical metastasectomy with surgical resection of hepatic, pulmonary, or adrenal metastases having improved rates of survival with resection [113–115]. Furthermore, systemic therapy may convert patients with widely metastatic disease to a limited volume metastatic state, increasing the proportion of patients who may be candidates for early treatment of oligometastatic disease. Surgical metastasectomy is the standard of care in patients who are candidates; however, this is available only to approximately a quarter of patients with hepatic metastases due to the extent of disease or comorbidities [116]. RFA and TACE, much like utilized in hepatocellular carcinoma, are treatment options for patients with hepatic metastases as well.

Noninvasive treatment of hepatic metastases is also possible with external beam radiotherapy. Stereotactic body radiotherapy has allowed the delivery of high doses of therapy in single and multiple fractions with excellent rates of local control. A multi-institutional Phase I/II trial from the University of Colorado enrolled patients with 1–3 liver metastases from any solid tumor, cumulative maximum tumor diameter <6 cm, adequate liver and kidney function, and no chemotherapy 14 days before or after SBRT [47]. In the Phase I portion, the SBRT/SABR dose was escalated from 36 to 60 Gy in 3 fractions. Thirteen patients were treated with a dose of less than 60 Gy and 36 patients treated at 60 Gy, for a total of 63 hepatic lesions. Volume delineation was similar to that in the lung oligometastases trial, with the PTV defined as GTV expanded by 5 mm radially and 10 mm craniocaudally and 7 mm radially and 15 mm craniocaudally, with active breathing control and abdominal compression, respectively. At least 700 cc of normal liver had to receive a total dose <15 Gy, and the sum of the left and right kidney volume receiving 15 Gy had to be less than 35 %. With a median follow-up of 16 months, the 2-year actuarial in-field local control was 92 % with a median overall survival of 20.5 months. Treatment was well tolerated with one patient suffering grade 3 soft-tissue toxicity, no grade 4 or 5 toxicity, and no instances of radiation-induced liver dysfunction (RILD).

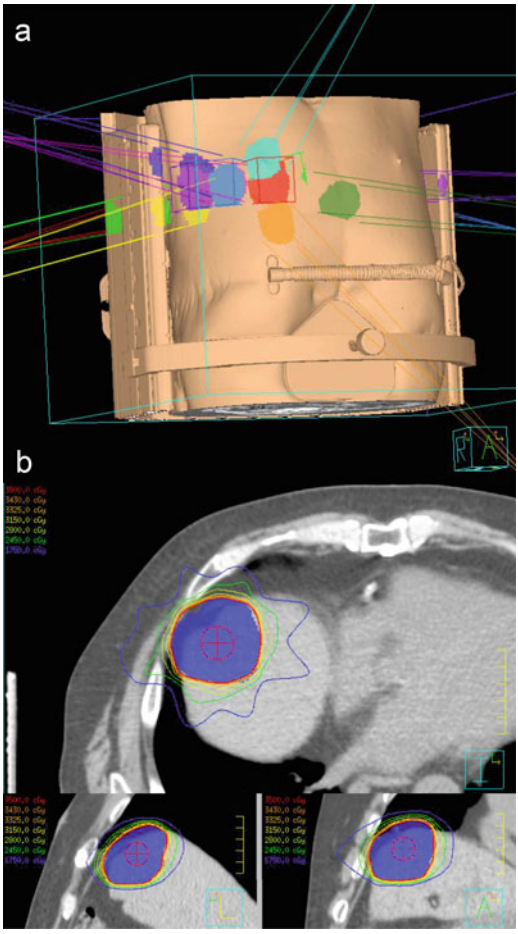

Fig. 8.2 Stereotactic body radiation therapy (SBRT) of a colorectal liver metastasis. (**a**) Beam arrangements for treatment of liver dome lesion. Diaphragmatic motion was limited by the use of a compression plate on the abdomen. (**b**) Dose distributions for treatment of large lesion in liver dome in axial, sagittal, and coronal planes, receiving 35 Gy in a single fraction

Recently, interest has been increased in the delivery of single-fraction liver SBRT/SABR. Wulf et al. demonstrated that single-fraction doses of 26 Gy improved local control at 12 months to approximately 100 % with no grade 3 or higher toxicity [117]. More recently, SBRT/SABR was successfully escalated to 40 Gy in a single fraction with no grade 3 or higher toxicities related to treatment observed [118]. Furthermore, the 36-month rate of local control was 100 % showing an excellent opportunity to control liver metastases. Figure 8.2 shows dosimetry and beam geometry for single-fraction liver SBRT/SABR.

Specific Issues Associated with SBRT/SABR for Targets in the Liver

Liver SBRT/SABR for metastatic disease is often performed in patients without concomitant cirrhosis. Nonetheless, normal liver reserve, much like surgical resection, is a key consideration with treatment planning, with a minimal residual functional volume of approximately 700 cc desired. In patients with HCC, the doses delivered, as seen above, are lower than for metastatic disease due to the sensitive, cirrhotic liver.

Traditional SBRT/SABR is delivered via photon beams with energies between 6 and 18 MV. Patient immobilization is a key factor in the delivery of stereotactic treatment, with stereotactic frames with reference to the stereotactic coordinate system, a commonly utilized system. Motion management for treatment of the liver is essential, given the considerable motion of the organ and diaphragm. During CT simulation, the movement of the dome of the diaphragm should be visualized via fluoroscopy or alternative means with techniques to limit motion including breath-hold and abdominal compression. Target volume delineation of liver lesions is ideally done with registration of an abdominal MRI, done in the treatment planning position with motion management, if possible. Planning can be performed with noncoplanar 3D-conformal techniques, intensity-modulated radiation therapy, or volumetric-modulated arc therapy. Prescription isodose lines covering the PTV are between 60 and 90 %, and suggested dose constraints for adjacent normal structures for 1, 3, and 5 fractions are shown below in Table 8.1.

SBRT/SABR for the Treatment of Prostate Cancer

Prostate cancer is the most common cancer in Western males after non-melanomatous skin cancer [36]. Among males, prostate carcinoma was the second leading cause of cancer mortality behind lung cancer. About 60 % of prostate cancer is diagnosed in men age 65 or older which impacts therapy options as a result of competing comorbidities. With introduction of PSA screening, the majority of prostate cancer is diagnosed in organ-confined disease, which is typically treated with radical prostatectomy or radiotherapy [119]. Dose escalation of conventionally fractionated external beam radiation therapy (CF-EBRT) has demonstrated improved biochemical control and even a survival advantage for patients with intermediate and high-risk disease [120–122]. These results can be achieved with acceptably low toxicity using modern conformal techniques, however, at the increased cost and inconvenience of delivering a large number of fractions, 5 days a week over 8–9 weeks. Additionally, the potential unusual radiobiological characteristics of prostate cancer suggest that it may be more sensitive to larger fractions of radiation. More hypofractionated regimens have been proposed to improve the efficacy and convenience of treatment for prostate cancer.

Table 8.1 Proposed dose constraints for SBRT/SABR treatments of 1, 3, and 5 fractions

Serial tissue	Volume (cc)	Volume max (Gy)	Max point dose (Gy)[a]	Endpoint (≥grade 3)
One fraction				
Spinal cord and medulla	<0.35	10	14	Myelitis
Esophagus[b]	<5	11.9	15.4	Stenosis/fistula
Heart/Pericardium	<15	16	22	Pericarditis
Rib	<5	28	33	Pain or fracture
Skin	<10	25.5	27.5	Ulceration
Stomach	<5	17.4	22	Ulceration/fistula
Bile duct			30	Stenosis
Duodenum[b]	<5	11.2	17	Ulceration
	<10	9		
Jejunum/ileum[b]	<30	12.5	22	Enteritis/obstruction
Colon[b]	<20	18	29.2	Colitis/fistula
Parallel tissue	**Critical volume (cc)**	**Critical volume dose max (Gy)**		
Liver	700	11		Basic liver function
Renal cortex (right and left)	200	9.5		Basic renal function
Serial tissue	**Volume (cc)**	**Volume max (Gy)**		
Three fractions				
Spinal cord and medulla	<0.35	15.9	22.5	Myelitis
Esophagus[b]	<5	17.7	25.2	Stenosis/fistula
Heart/pericardium	<15	24	30	Pericarditis
Rib	<5	40	50	Pain or fracture
Skin	<10	31	33	Ulceration
Stomach	<5	22.5	30	Ulceration/fistula
Bile duct			36	Stenosis
Duodenum[b]	<5 <10	15.6 12.9	22.2	Ulceration
Jejunum/ileum[b]	<30	17.4	27	Enteritis/obstruction
Colon[b]	<20	24	34.5	Colitis/fistula
Parallel tissue	**Critical volume (cc)**	**Critical volume dose max (Gy)**		
Liver	700	17.1		Basic liver function
Renal cortex (right and left)	200	15		Basic renal function
Serial tissue	**Volume (cc)**	**Volume max (Gy)**		

(continued)

Table 8.1 (continued)

Serial tissue	Volume (cc)	Volume max (Gy)	Max point dose (Gy)[a]	Endpoint (≥grade 3)
Five fractions				
Spinal cord and medulla	<0.35	22	28	Myelitis
Esophagus[b]	<5	19.5	35	Stenosis/fistula
Heart/pericardium	<15	32	38	Pericarditis
Rib	<5	45	57	Pain or fracture
Skin	<10	36.5	38.5	Ulceration
Stomach	<5	26.5	35	Ulceration/fistula
Bile duct			41	Stenosis
Duodenum[b]	<5	18.5	26	Ulceration
	<10	14.5		
Jejunum/ileum[b]	<30	20	32	Enteritis/obstruction
Colon[b]	<20	28.5	40	Colitis/fistula
Parallel tissue	**Critical volume (cc)**	**Critical volume dose max (Gy)**		
Liver	700	21		Basic liver function
Renal cortex (right and left)	200	18		Basic renal function

[a]"Point" defined as 0.035 cc or less
[b]Avoid circumferential irradiation

CF-EBRT schemes employing fraction sizes of 1.8–2.0 Gy are based on the premise that tumors are less responsive to faction size than are late-responding normal tissues. The α/β ratio is a measure of fractionation response with low ratio typically associated with late-responding tissues (normal tissues) and higher ratios associated with acute-responding tissues (tumors). Convention states that a low α/β ratio is consistent with a higher capacity for repair between fractions with an accompanying greater relative sparing with smaller fraction sizes. Therefore under these conditions, an improved therapeutic ratio would be achieved with multiple small fractions for most tumor types. However, if a tumor has a lower α/β ratio than surrounding organs, decreasing dose per fraction preferentially spares the tumor, suggestion that for tumors with a low α/β, hypofractionation may be more effective [57].

Recent analysis and review of clinical outcomes, primarily after treatment with brachytherapy, argue for a low α/β for prostate cancer of approximately 1.5 [123–127]. Several recent clinical trials were designed with the explicit assumption of this low α/β ratio by utilizing more hypofractionated regimens in comparison with conventional schedules [128–133]. Altogether, these trials show that the treatment can be delivered much more quickly and conveniently using equivalent effective doses with hypofractionation without compromising PSA control or significant toxicity so long as careful technique and normal tissue dose tolerance are respected. Building upon this premise, even more extreme hypofractionated approaches (6.5–10 Gy per fraction) have been investigated.

Madsen et al. published one of the first experiences with prostate SABR describing their results from a Phase I/II trial at the Virginia Mason Medical Center [134]. Forty men with low-risk disease (Gleason score ≤6, PSA <10 ng/mL, and clinical stage ≤T2a) were treated with 5 fractions of 6.7 Gy per fraction for a total dose of 33.5 Gy. The target was the prostate plus a 4–5 mm margin. Daily image guidance was used using implanted fiducial markers. Median follow-up was 41 months. There was one acute grade 3 urinary toxicity (urinary retention requiring catheterization) and no acute grade 4–5 toxicities. Late grade 2 GU and GI toxicity rates were 20 % and 7.5 %, respectively, with no grade 3 or higher toxicities. Four-year actuarial freedom from biochemical recurrence (FFBR) was 90 %.

The feasibility of increasing SBRT/SABR dose was investigated by King et al. at Stanford University in a Phase II trial [135]. 36.25 Gy in 5 fractions of 7.25 Gy was delivered to the prostate plus a 3–5 mm margin. In 67 patients with low- to intermediate-risk features (Gleason score 3 + 3 or 3 + 4, PSA ≤10 ng/mL, and clinical stage ≤T2b), there were no grade 4 or higher toxicities. Late grade 2 and 3 GU toxicity rates were 5 % and 3.5 %, respectively. Late grade 2 GI toxicity was 2 % with no grade 3 or higher toxicities seen. Patients who received QOD treatments were less likely to experience grade 1–2 GI and GU toxicities than those who received QD treatments. Four-year PSA relapse-free su rvival was 94 %.

The largest prospective study of prostate SBRT/SABR is from Katz et al. at the Winthrop University Hospital [136]. Three hundred four patients (69 % low-risk, 27 % intermediate-risk, 4 % high-risk) were treated. The first 50 patients received 35 Gy in 5 fractions of 7 Gy with the subsequent 254 patients receiving 36.25 Gy in 5 fractions of 7.25 Gy. Lower-dose patients had a median follow-up of 30 months and the higher-dose patients a median follow-up of 17 months. There were no grade 3–4 acute complications. Late grade 2 GU and GI toxicities were 14 % and 7 %, respectively. Five patients had late grade 3 GU toxicity with no late grade 4–5 toxicities. For patients that were potent prior to treatment, 75 % stated that they remained sexually potent. Actuarial 5-year biochemical recurrence-free survival was 97 % for low-risk, 90.7 % for intermediate-risk, and 74.1 % for high-risk patients.

A recent pooled analysis of 1100 patients from prospective Phase II trials using SBRT/SABR for the treatment of prostate cancer in which a median dose of 36.25 Gy was delivered in 4–5 fractions demonstrated a 93 % 5-year biochemical relapse-free survival rate for all patients (95 % for low-risk, 84 % for intermediate-risk, and 81 % for high-risk) with favorable long-term patient-reported outcomes with respect to urinary and bowel functions [137, 138].

Compared to the prior studies using similar dose fractionation regimens, we commenced a multicenter Phase I/II trial investigating using significantly higher doses [139]. We chose to start at a dose similar to the biologic equivalent margin dose of the HDR brachytherapy experience (i.e., 45 Gy in 5 fractions) and escalate to 50 Gy in 5 fractions. In the Phase I portion, 45 patients, in 3 cohorts of 15, were treated with 45, 47.5, and 50 Gy in 5 equal fractions, respectively. Forty percent had low-risk disease (Gleason score ≤6, PSA <10 ng/mL, and clinical stage ≤T2a) and 60 % with intermediate-risk (Gleason score = 7 or PSA >10 ng/mL, <15 ng/mL, or

clinical stage T2b). No dose-limiting toxicities (grade 3–5) occurred within the first 90 days posttreatment. GI grade ≥2 and grade ≥3 toxicity occurred in 18 % and 2 %, respectively, and GU grade ≥2 and grade ≥3 toxicity occurred in 31 % and 4 %, respectively. Initial PSA control was 100 %. These encouraging results led to the further enrollment on the Phase II trial at the 50 Gy dose level studying late toxicity. An additional 46 patients were enrolled for a total of 91 (64 % intermediate-risk and 36 % low-risk). With a median follow-up of 42 months, PSA control remained at 99 % [140]. One patient with unfavorable intermediate-risk disease, who was treated on the 45 Gy arm, demonstrated failure to therapy.

Specific Issues Associated with SBRT/SABR for Targets in the Prostate

Ultimately, dose escalation to treat prostate cancer is limited by toxicity to the bladder or rectum. As reported in an update by Kim et al., the toxicity profile was favorable in the initial Phase I results; however, in the Phase II portion, the profile changed and five patients (10.6 %) developed high-grade rectal toxicity [141]. Injury was primarily to the anterior rectal wall and required a diverting colostomy for resolution.

Dosimetric analysis was performed on treatment planning data to determine predictors for rectal tolerance when using SBRT/SABR [141]. We predicted that the key to tolerance for SBRT/SABR would relate to the degree of damage inflicted and the success of normal tissue injury repair permitted. The most successful surgical repair of radiation-induced rectal injury with deep ulceration and/or fistula is by inserting a myocutaneous graft. A myocutaneous graft provides both a blood supply to devascularized areas via transferred muscle (i.e., the myo-component) as well as epithelial stem cells via skin and mucosal grafting (i.e., the cutaneous component) capable of proliferation over the denuded areas. We hypothesized that the two primary physiological requirements learned from surgical repair studies, a robust blood supply and adequate stem cells capable of repairing mucosal injury, are impaired by high dose of radiation therapy, and therefore, injuries would primarily fall into two categories: (1) mucosal damage including injury to stem cells and/or (2) vascular/stromal damage leading to devitalization of tissues. In turn, the inability to heal may be due to (1) stem cell (crypt cell) depletion at the site of injury and inability to efficiently recruit neighboring viable stem cells, due to excessive distance required to migrate to the site of injury, and/or (2) significant destruction of stroma and vasculature by excess volume of rectal wall being irradiated to an ablative dose of radiation. In line with this hypothesis, high-grade rectal events were correlated with the volume of rectal wall receiving 50 Gy >3 cm^3 and treatment of >35 % of rectal wall to 39 Gy (Fig. 8.3a, b). Additionally, a high rate of acute grade ≥2 rectal injury occurred if more than 50 % of the rectal mucosa was irradiated beyond 24 Gy. Therefore, strategies of limiting percent rectal circumference (PRC)

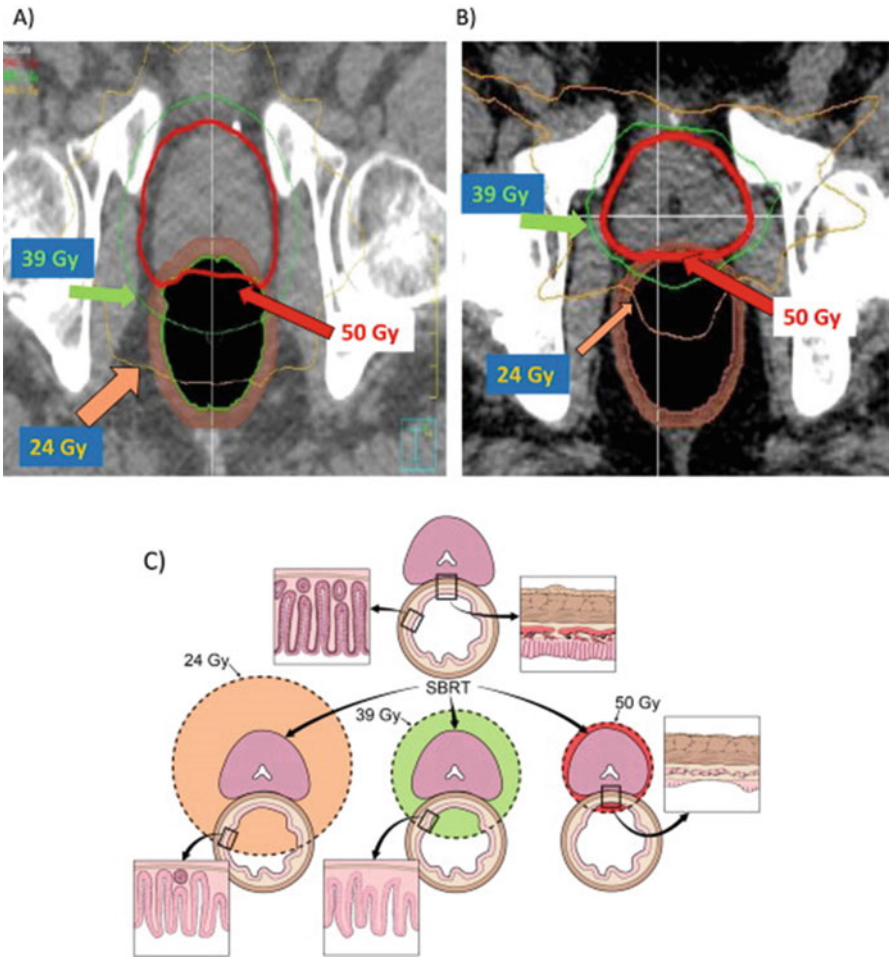

Fig. 8.3 Determination of rectal toxicity when treating the prostate with ablative doses. Representative treatment plans of patients treated with 50 Gy in 5 fractions. (**a**) Experienced grade 2 acute and grade 3 late rectal toxicity. (**b**) Only experienced grade 1 acute/late rectal toxicity. (**c**) Potential biological consequence of rectal wall irradiation. (Reprinted with permission from [141])

treated to 24 Gy may reduce risk of acute grade ≥2 rectal events, whereas reducing PRC treated to 39 Gy may reduce the risk of high-grade late rectal toxicity (Fig. 8.3c).

In an attempt to optimize treatment planning and reduce rectal toxicity, we are currently investigating the use of a biodegradable spacer to increase the distance between the target organ (prostate) and the tissue at risk (rectum). This spacer has been shown to be well tolerated and able to reduce patients experiencing declines in bowel and urinary quality of life when used with conventionally fractionated image-guided radiation therapy [142–144]. These spacers would likely be particularly

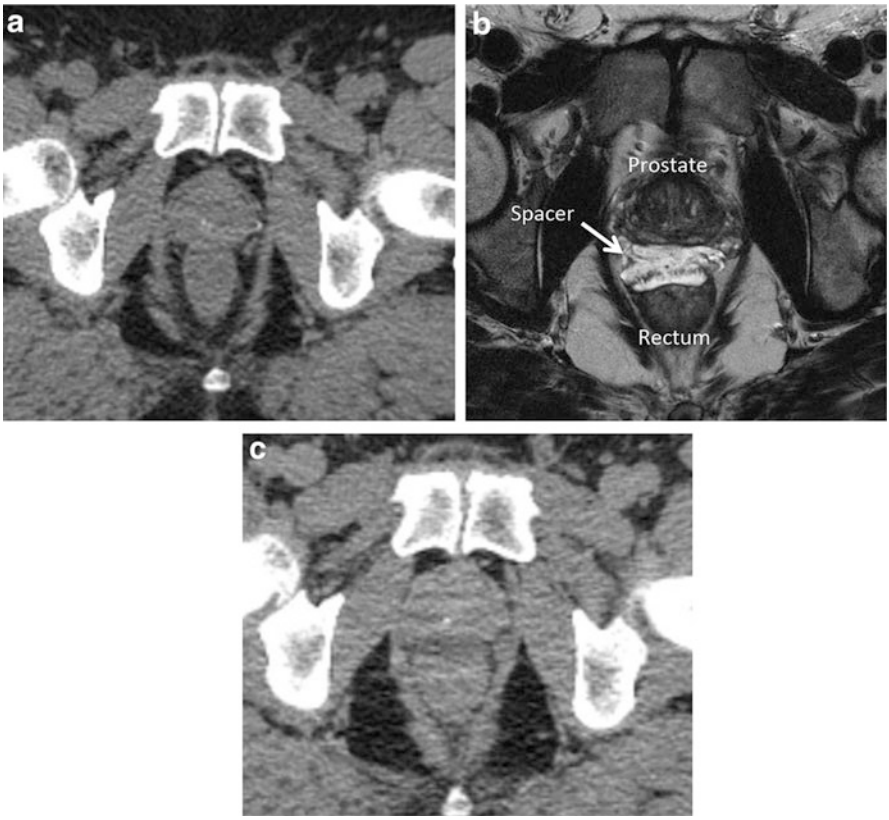

Fig. 8.4 Increased separation with the use of a biodegradable spacer (SpaceOAR system; Augmenix, Waltham, MA). (**a**) Planning computer tomography (CT) axial imaging prior to spacer placement. (**b**) T2-weighted axial magnetic resonance images and (**c**) planning CT axial imaging post spacer placement

effective at reducing the high dose associated with vascular/stromal injury and will likely lead to significant reduction of high-grade rectal toxicity events while allowing the highly effective tumor ablative dose to be delivered, thereby increasing the therapeutic ratio (Fig. 8.4).

Conclusions

Through advances in imaging and radiation delivery techniques, the use of stereotactic radiation in the body has become a common treatment approach in a relatively quick fashion. Well-conducted clinical studies have shown that SBRT/SABR can be utilized for a broad scope of indications, especially for the eradication for gross

primary disease. In addition, due to its oligofractionation approach, SBRT/SABR can easily integrate into systemic therapeutic regimens without causing significant delays or disruptions. Further investigation of the potential immunological stimulation of ablative radiation could lead to more efficacious therapies, especially for the treatment of metastatic disease. Going forward, ablative therapies utilizing particles will be of increased interest due to the potential for increased sparing of normal tissue dose and higher radiobiological potency.

Disclosures
The authors have reported no relevant financial disclosures.

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