Stereotactic body radiation therapy (SBRT) is a rapidly evolving cancer treatment method in which concepts and techniques previously developed for brain tumor radiosurgery are adapted to eradicate tumors elsewhere in the body. The spatial accuracy, conformality, and steep radiation dose gradients of radiosurgery, which have been critical to its success in the treatment of intracranial tumors, are applied in SBRT to treat a variety of extracranial tumors. Early results demonstrate excellent response rates and low toxicity with a variety of hypofractionated dose regimens and localization/immobilization techniques. This article provides an overview of the rationale and results of SBRT for specific indications, descriptions of some methods of treatment delivery, and discussion of potential areas of future investigation.

Stereotactic radiosurgery (SRS) is a term originally created by Lars Leksell to describe a new approach to radiotherapy for brain tumors using multiple convergent beams, precise localization via a stereotactic coordinate system, rigid patient immobilization, and singlefraction treatment. The technique contrasts sharply with conventional three-dimensional (3D) conformal external-beam radiotherapy (CRT), in which the total radiation dose is given in numerous—often 25 or more—small daily doses or fractions. The dose-fractionation allows for repair in normal tissues between fractions, but the need to reproduce the patient's initial positioning on multiple occasions necessitates the inclusion of an extra margin of normal tissue around the tumor in the treatment field to account for daily set-up variations. With SRS, a stereotactic immobilization frame is tightly pinned to the patient's skull, allowing the spatial precision for treating with zero to minimal margin of surrounding tissue. The resulting reduction in volume of normal tissue irradiated leads to the ability to deliver higher doses, thereby potentially improving tumor control. Positive clinical experience accumulated over the past 2 decades has affirmed the utility of SRS in the treatment of a variety of intracranial tumors. For brain metastases, treatment with SRS lengthens median survival compared to conventional radiotherapy,[1] and for other clinical entities (eg, arteriovenous malformations, trigeminal neuralgia, acoustic schwannomas), SRS has offered a valuable new alternative to surgery.[2] Recent advances in 3D-CRT include alterations in the treatment schedule to shorten the length of treatment as well as modulation of the intensity of the radiation beam profile, either to provide selective boost doses to gross disease within a larger field or to minimize the radiation dose to irregularly shaped normal tissues adjacent to the area treated. However, these approaches have changed the daily or fractional dose by a very limited proportion relative to conventional doses, and the capability of delivering higher fractional doses in the radiosurgical range have not been previously tested. The anatomic characteristics of the skull and stability of cranial contents make SRS feasible for intracranial tumors, but the lack of a similar fixed bony reference structure as well as respiration-induced movement creates difficulty for application outside the cranium. In 1994, Lax et al of the Karolinska Institute reported a method for performing what is now called stereotactic body radiation therapy (SBRT) for abdominal malignancies, using a custom body cast with stereotactic coordinates.[3] Blomgren and Lax subsequently reported an 80% progression-free rate in 42 tumors of the lung, liver, or abdomen treated with this method to mean doses of 30 Gy delivered in one to four fractions.[4] Since this report, there has been increasing interest in and reports on the use of a similar approach of spatially precise, single-dose treatment or very brief regimens involving typically three to five individual doses (hypofractionation). The principles that have generally been used in the selective application of SBRT mirror those of SRS. Treatment is limited to small- to moderate-volume discrete tumor targets. Prophylactic coverage of the surrounding region of potential microscopic disease is not performed, thereby maintaining a simple volume and eliminating dose gradients between spatially separated target structures. Targets are within radiosensitive normal tissue or surrounding structure with parallel (as opposed to serial) architecture, where small portions of normal tissue surrounding the structure can receive high doses of radiation without clinical consequences due to functional reserve of unaffected organ. A dose-response relationship should be exploited using the capacity for increased dose delivery offered by SBRT. In this paper, we describe the methods used in treating patients with "extracranial
radiosurgery,” “extracranial radiotherapy,” or SBRT, the clinical scenarios in which it is applicable and why, and unresolved issues and future directions for investigation. **Physics and Technology of SBRT** For single high-dose or hypofractionated SBRT, it is necessary to maintain a higher confidence in radiation dose delivery than with 3D-CRT. Several methods have been used to achieve spatial accuracy during SBRT, and herein are discussed methods that have been described in published reports of patients treated with hypofractionated, high-dose radiation and multiple beams. The term stereotactic implies the use of an external frame of reference indexed to internal volumes to be targeted. Not all of the methods necessarily utilize strict stereotactic localization methods, but the term stereotactic has been a common denominator when describing this literature as a whole. In general, the sequence of events for patients undergoing SBRT include the following: (1) computed tomography (CT) simulation, (2) immobilization, (3) planning, (4) repositioning, (5) relocalization, and (6) treatment delivery. The CT simulation is used to assess tumor size, location, and range of motion and to determine if the patient can tolerate the planned immobilization. During the initial CT, the range of tumor motion observed provides the necessary data for the required margin to be added around the gross target volume to define the planning target volume—the actual volume to be targeted in order to be certain that the gross target volume receives the full intended dose during each treatment. Immobilization includes a custom-fitted device to minimize motion and breathing effects, and provide a reproducible setup. The planning must address the small-field dosimetry issues common to cranial stereotactic radiosurgery but with the additional focus of inhomogeneity corrections for lung fields, and volumetric considerations for normal tissue complications of the critical organ being treated (ie, lung or liver). Repositioning addresses the accurate setup of the patient in the planned position, whereas relocalization addresses the specific identification of the tumor and planned isocenter in the treatment field. Finally, treatment delivery is performed using any of a wide array of high-precision beam delivery techniques, including mini-multileaf collimation, gantry mounted linear accelerators (linacs), and combined imaging and treatment units. **Patient Immobilization, Positioning, and Relocalization** All of the reports on SBRT have included a CT simulation to assess tumor location, size, range of motion, and feasibility of treatment within the established parameters of the particular institute. Lax's initial report involved the use of a body cast within a rigid box frame with radio-opaque scale markers for acquisition of imaging data. The scales mounted on the frame, corresponding to fiducials, were used to establish a coordinate system in the 3D space of the treatment room. Diaphragmatic movement was limited by using a plate applying pressure on the abdomen.[3] Blomgren's mean reproducibility for 75 evaluable tumors was reported as 3.7 mm in the transverse plane and 5.7 mm longitudinal; a margin of 5 mm was added to the gross target volume in the transverse plane and a margin of 10 mm was added in the longitudinal direction to define the planning target volume.[4] Since the report of the Karolinska's treatment method, some institutions have used the same technique of a body frame with diaphragmatic pressure plate and stereotactic coordinates to treat lung and liver tumors (eg, Leibinger frame, Elekta frame), while others have used a variety of immobilization and repositioning methods in attempts to achieve similar accuracy. Overall, the reported accuracy is within 5 mm for the various methods utilized. A comprehensive evaluation of these methods is beyond the scope of this paper, but Table 1 lists some of the methods used; select methods are described in more detail below.[3,5-17]
Sato et al described a frameless stereotactic technique for metastatic liver cancer in which 14 patients were instructed to keep shallow respiration with an oxygen mask and abdominal belt on the treatment table.[5] Patients received transcatheter arterial chemoembolization with lipiodol, which played a role as a radio-opaque marker for x-ray simulation and CT monitoring. Relocalization accuracy was performed with a multifunctional unit incorporating CT scanner, x-ray simulator, and linac sharing one treatment couch. Patients underwent imaging and target localization prior to each daily treatment without getting off the couch between scan and treatment. No overall statistics on the patient immobilization and tumor relocalization were reported.[5] Nakagawa et al utilized a similar approach of immediate pretreatment image verification with a megavoltage (6-MV) CT scanner mounted on a linac.[6] Hara et al employed a method of transferring the patient to the treatment unit within a custom bed after a CT scan was performed to place the isocenter; treatment was performed with respiratory gating.[7] The CyberKnife (Accuray, Sunnyvale, Calif) consists of a gantry-mounted linac coupled with a realtime image guidance system. The treatment site is imaged by two x-ray fluoroscopes and bony landmarks are referenced to the components of the hardware. Once the location of the bony landmark has been determined relative to the robot arm, the position of the tumor is accounted for and adjusted accordingly. The cameras can frequently update the body position and accommodate for patient motion and setup changes, and in that regard, this device has six degrees of freedom allowing for volumes with more complex shapes. Murphy reported a mean total radial error of 1.6 mm and found that the accuracy of the system was equal to or better than that of frame-based systems currently in use.[8]
Whereas the Lax system was designed to treat soft-tissue tumors, Hamilton et al described a system for spinal cord irradiation for extracranial stereotactic radiosurgery using a screw fixation technique.[9] The Hamilton system was based on the principles of rigid skeletal fixation. A rigid box is used for the patient to lie prone and a clamp is fixated on the surgically exposed spinous process above and below the target areas. Once the coordinates of the target have been acquired from the CT images, the box is transferred to the linac treatment table and aligned using standard lasers. The clinical experience with this frame has shown reproducibility on the order of 2 mm. Primary Lung Tumors Several reports have described the treatment of early-stage primary non-small-cell lung cancer (NSCLC) with SBRT. Although surgical resection is the primary modality of treatment, radiotherapy has been used in patients who are not medically fit to undergo surgery. Survival rates among patients who received 3D-CRT are generally inferior to those of surgery, but selection bias likely plays a role on the observed difference, since patients referred for 3D-CRT usually have significant intercurrent illness. The use of higher doses has been associated with improved outcomes.[18,19] Sibley summarized the results of CRT in patients with T1/2, N0 tumors, concluding that elective

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Median Follow-up</th>
<th>Local Control</th>
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<tbody>
<tr>
<td>Timmerman et al, 2003[16]</td>
<td>37</td>
<td>15 mo</td>
<td>83%</td>
</tr>
<tr>
<td>Uematsu et al, 2003[26]</td>
<td>43</td>
<td>20 mo</td>
<td>100%</td>
</tr>
<tr>
<td>Nagata et al, 2002[13]</td>
<td>31</td>
<td>16 mo</td>
<td>100%</td>
</tr>
<tr>
<td>Wulf et al, 2001[25]</td>
<td>12</td>
<td>8 mo</td>
<td>85%</td>
</tr>
<tr>
<td>Hara et al, 2003[7]</td>
<td>5</td>
<td>20 mo</td>
<td>100%</td>
</tr>
<tr>
<td>Hof et al, 2003[14]</td>
<td>10</td>
<td>15 mo</td>
<td>80%</td>
</tr>
<tr>
<td>Onimaru et al, 2003[27]</td>
<td>19</td>
<td>17 mo</td>
<td>85% (2 yr)</td>
</tr>
</tbody>
</table>

SBRT = stereotactic body radiation therapy.

Table 3
Comparison of Biologic Equivalent Doses* of Fractionation Regimens Used in Radiotherapy vs SBRT for Early-Stage Non–Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose</th>
<th>Equivalent Dose In 2-Gy Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard radiotherapy</td>
<td>2 Gy × 30–33</td>
<td>60–66 Gy</td>
</tr>
<tr>
<td>Timmerman et al, 2003[16]</td>
<td>20 Gy × 3</td>
<td>150 Gy</td>
</tr>
<tr>
<td>Onimaru et al, 2003[27]</td>
<td>7.5 Gy × 8</td>
<td>87 Gy</td>
</tr>
<tr>
<td>Hara et al, 2003[7]</td>
<td>30 Gy × 1</td>
<td>100 Gy</td>
</tr>
</tbody>
</table>

* Linear quadratic method, alpha/beta = 10.
nodal irradiation was unwarranted and higher doses were associated with improved tumor control and disease-free survival.[20] Although 3D-CRT doses of 60 to 66 Gy were not associated with radiation pneumonitis in this review, a study by Langendijk et al suggests that 3D-CRT may negatively affect quality of life.[21] Patient-reported quality of life was assessed at intervals starting prior to radiotherapy in 46 patients, and showed worsening trends in dyspnea, appetite, and fatigue up to 24 months posttherapy. Despite the fact that progression of medical comorbidities is common in this population, the worsening trend was seen to begin at 2 weeks into therapy. Dysphagia was the only symptom that was statistically different between patients treated to locoregional fields vs those receiving treatment to the lung primary alone. Reports of SBRT in early-stage NSCLC describe doses that are biologically higher than doses used in 3D-CRT. Based on tumor control probability calculations derived from a database of patients treated with conventional techniques, Martel et al predicted that a dose of 84 Gy (in 2-Gy fractions) was necessary to achieve local progression-free survival in 50% of patients.[22] However, any dose-escalation scheme using convention-al fractionation requires an increase in overall treatment time, which has been negatively correlated with tumor control rates and patient outcomes.[23] Randomized clinical evidence supports the use of a shortened treatment duration (accelerated fractionation) in NSCLC, albeit at a cost of increased pneumonitis with CRT.[24] Numerous series have documented the efficacy and safety of SBRT in the treatment of early-stage NSCLC (see Table 2).[7,13,14,16,25-27] Although median follow-up durations are short, local control rates are high and compare favorably with those for conventional treatment. Due to the large differences in fraction sizes between SBRT and conventional treatment, direct comparison of total nominal doses is not feasible. The linear quadratic method is generally accepted for drawing comparisons between different fractionation schemes. Table 3 compares the biologic effective dose of the two types of treatment, assuming an alpha/beta ratio of 10.[7,13,16,27,28] One can readily see that the biologic effective doses for SBRT are higher than the standard 60 to 66 Gy for conventional therapy. Despite the use of higher doses than typically given, SBRT has not been associated with an increased rate of complications. Table 4 summarizes the toxicities described in the literature for SBRT in patients with lung tumors (both NSCLC and metastatic), with the reported incidence of grade 3 toxicities generally less than 5%. [4,6,7,13,14,25-27,29] Fukumoto performed routine pulmonary function testing before and after treatment and found no decline in median forced expiratory volume in 1 second (FEV1) or diffusing capacity of the lung for carbon monoxide (DLCO) values following therapy.[15] Given that a dose-response relationship exists for NSCLC, and SBRT has been found to have little associated toxicity, dose-escalation studies are needed. Timmerman et al have performed the only dose-finding study for SBRT thus far.[16] A total of 36 patients with medically inoperable stage I NSCLC were treated in a phase I study using a three-fraction regimen, starting at 8 Gy per fraction. The technique employed was the same as that of the Karolinska Institute. Dose was safely escalated to 20 Gy per fraction (total dose: 60 Gy), with the maximal tolerated dose not reached. Toxicity consisted of one case of grade 3 pneumonitis and one case of grade 3 hypoxia; pulmonary function testing revealed no statistically significant changes following treatment. Radiographic response was seen in 87% of patients. At a median follow-up of 15 months, there were 6 local failures, all occurring in patients treated with less than 18 Gy per fraction.[16]
Despite the stated potential advantages of SBRT, a similar dose-escalation study using CRT has not been performed in this patient population. Thus, one cannot exclude the possibility of similar results being achievable with higher doses of CRT. **Lung Metastases** Most series describing SBRT for lung tumors include patients treated for metastatic disease. Dose-fractionation schemes and techniques employed are similar to those for primary lung tumors, and control rates range from 66% to 100% with minimal reported toxicity (see Table 5).[4,6,7,13,25-27] Although radiotherapy has not traditionally been employed in curative fashion for these patients due to perceived poor prognosis, data exist to support aggressive local therapy for selected patients with lung metastases.[30] The International Registry of Lung Metastases reported the largest series to date of surgical metastasectomy in 5,206 cases from 18 institutions in Europe and North America. Primary histology was epithelial in 2,260 cases, sarcoma in 2,173, germ cell in 363, and melanoma in 328. With a median follow-up of 35 months, actuarial survival after complete metastasectomy (achieved in 88% of patients) was 36% at 5 years and 26% at 10 years. Multivariate analysis showed better prognosis for patients with a single metastasis, disease-free intervals of 36 months or more, and germ cell tumors, although long-term survivors were seen in all histologic types.[31] Some series of surgical metastasectomy have also found tumor size and nonmelanoma histology to be of prognostic significance, although others report no differences.[30,32] Given the high rates of local control and low toxicity demonstrated for SBRT, similarly selected patients who are not otherwise eligible for surgery may receive comparable benefit from treatment with SBRT and should be considered for

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Dose</th>
<th>Grade 3 Toxicity</th>
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<tbody>
<tr>
<td>Uematsu et al, 2003[26]</td>
<td>66</td>
<td>30–76 Gy, 5–15 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Nakagawa et al, 2000[6]</td>
<td>22</td>
<td>15–24 Gy, 1 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Nagata et al, 2002[13]</td>
<td>40</td>
<td>40–48 Gy, 4 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Wulf et al, 2001[25]</td>
<td>61</td>
<td>26–37.5 Gy, 1–3 fx</td>
<td>3%</td>
</tr>
<tr>
<td>Hara et al, 2003[7]</td>
<td>23</td>
<td>20–30 Gy, 1 fx</td>
<td>4%</td>
</tr>
<tr>
<td>Hof et al, 2003[14]</td>
<td>10</td>
<td>19–26 Gy, 1 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Onimaru et al, 2003[27]</td>
<td>57</td>
<td>48–60 Gy, 8 fx</td>
<td>2%</td>
</tr>
<tr>
<td>Whyte et al, 2003[29]</td>
<td>23</td>
<td>15 Gy, 1 fx</td>
<td>0%</td>
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</table>

**SBRT** = stereotactic body radiation therapy.
Liver Metastases Secondary spread of cancer to the liver is a common occurrence and represents an important clinical problem.[33,34] While minimal-volume disease isolated to the liver is infrequent, aggressive local therapies for selected patients have been associated with improvements in long-term outcome.[35] Surgery has been considered the gold standard treatment based on single-institution retrospective reports. In selected operable colorectal cases where complete surgical extirpation of hepatic disease is achieved, average 5-year survival rates of 30% have been reported.[36-39] However, hepatic metastasectomy is associated with significant morbidity and mortality, with a median length of hospital stay of 7 days and operative mortality of 5.8%.[40] Patients with hepatic metastases who undergo surgical resection are also highly selected, as they must be medically fit for surgery, have disease limited to the liver, and have adequate reserve of normal liver parenchyma for full recovery after resection of all clinically apparent liver disease. As a result, only 5% to 10% of patients are eligible for hepatic resection.[41] Therefore, the vast majority of patients with hepatic metastases are more ideally suited for nonsurgical therapy such as SBRT, radiofrequency thermal ablation, cryotherapy, intrahepatic chemotherapy, chemoembolization, or systemic chemotherapy. Systemic chemotherapy alone rarely achieves complete eradication of hepatic metastases. Radiofrequency thermal ablation and cryotherapy can be performed percutaneously, laparoscopically, or via open laparotomy, but all are invasive procedures requiring anesthesia and hospitalization. Radiofrequency thermal ablation complication rates are generally reported to range from 2% to 5%. Radiation therapy (both 3D-CRT and SBRT) has advantages over other local and regional therapies of being noninvasive and feasible for outpatient treatment.

Clinical Trials
University of Michigan investigators have reported one of the largest series of patients treated with 3D-CRT either for unresectable colorectal liver metastases or primary liver tumors and have shown that higher radiation dose is significantly associated with improved survival.[42,43] It is possible to maintain normal liver function while surgically removing 75% to 80% of the total hepatic parenchyma, supporting the concept that the liver is organized into functional subunits arranged in a parallel fashion with normal function maintained as long as there are sufficient subunits (ie, volume) remaining. The risk of hepatic radiation toxicity (radiation hepatitis) is also volume dependent, as well as dose dependent.[44] Dawson summarized toxicity results in 203 patients treated with CRT and hepatic arterial chemotherapy and observed for a minimum of 4 months, so that they were assessable for radiation-induced liver disease. A strong volume effect was observed, and there was significant correlation of mean dose to normal liver and incidence of radiation-induced liver disease, supporting the hypothesis that techniques that reduce the volume of liver irradiated may lead to the ability to increase doses and improve survival.[45] Blomgren and Lax's initial report included 14 patients with liver metastases and 8 patients with primary hepatic tumors. For this group, the total minimum dose to the planning treatment volume varied from 7.7 to 45 Gy in one to four fractions (7.7 to 20 Gy per fraction). Nausea and fever occurred a few hours after radiotherapy in the initial
patients but later were successfully prevented with antiemetics and antipyretics. A response occurred in 50% of tumors, and 80% had no progression within a followup period of 1.5 to 38 months.[4] Two patients with cirrhotic livers developed intractable ascites at 6 weeks, and another patient had a subcapsular bleed at 2 weeks. These same authors reported their 5-year experience in a separate report on 17 patients with 21 metastases (some overlap with the prior report) treated to doses of 20 to 40 Gy in two to four fractions.[46] During a mean follow-up of 9.6 months, growth arrest was observed in 10, reduction of tumor size in 4, and tumor disappearance in 4 (1/21 failures). Tumors were treated with five to nine beams planned to produce steep dose gradients outside the target volume. Toxicity was mostly limited to fever and nausea in patients treated to the liver, but two patients developed gastrointestinal complications (hemorrhagic gastritis and duodenal ulcer) due to cumulative doses of 20 Gy to the distal stomach and proximal duodenum, respectively. Based on this initial experience, German investigators performed a phase I/II single fraction stereotactic radiotherapy study for liver tumors.[17] A total of 60 liver tumors (56 metastases, 4 primary hepatic tumors) in 37 subjects were treated. Radiation dose was escalated from 14 to 26 Gy in one fraction prescribed to the 80% isodose line. Median tumor size was 10 cm$^3$ (range: 1 to 132 cm$^3$). During a median follow-up period of 5.7 months, 55 patients were evaluable. Treatment was well tolerated with no reported cases of radiation-induced liver disease. Local failure was identified in 12 of 55 (22%). There was a trend toward larger tumors in the uncontrolled group (mean size: 31 cm$^3$ in the uncontrolled group vs 19 cm$^3$ in the controlled group). Additional German experience using SBRT for liver and lung tumors was reported by Wulf.[25] Liver metastases accounted for 23 of the 24 liver lesions. A regimen of three 30-Gy fractions was prescribed to the 65% isodose line. Median follow-up was 9 months for the liver targets, and median planning target volume was 102 cm$^3$. Actuarial local control at 1 and 2 years which was defined as complete or partial regression and stable disease was achieved in 76% and 61%, respectively. There was no grade 3-5 acute or late toxicity in the irradiated liver group. The results of SBRT for liver tumors is summarized in Table 6.[4,5,17,25]

**Postirradiation Surveillance**

It should be noted that standard criteria for response may not be applicable in this setting as there are likely to be residual changes on CT, especially early after treatment. Reversible CT findings after radiotherapy have been described by Gouliamos, but further study of imaging changes after focal high-dose hepatic radiation treatment is required.[47] A recent report found that positron-emission tomography (PET) as surveillance after radiofrequency ablation was accurate in identifying recurrences and is likely to have similar utility in distinguishing viable tumor from scar in irradiated lesions.[48]

**In Summary**

SBRT for hepatic metastases is a noninvasive local therapeutic modality that has demonstrated safety and response. The most effective dose and fractionation schedule remains to be determined. However, if 1 to 5 large dose fractions are as effective as 10 to 30 fractions, with no increased toxicity, this would be more convenient for patients and should become the standard of care. Reports of SBRT involving treatment of liver tumors have included predominantly liver metastases, with few patients receiving treatment for primary liver tumors. Hepatocellular carcinoma presents challenges for SBRT due to its frequent subclinical multifocality as well as its tendency to arise in cirrhotic liver, which may be more sensitive to radiation hepatitis. However, existing evidence supports the role of local invasive therapies such as radiofrequency ablation or chemoembolization,
and radiation dose responsiveness has been demonstrated for these tumors, suggesting a potential role for SBRT in their management.[42,49] **Spinal and Paraspinal Tumors** Successful radiotherapy for spinal and paraspinal tumors has been limited by the relative sensitivity of spinal cord to radiation injury and the low acceptable threshold for complications. Tumors located within this area lend themselves to SBRT by virtue of their close association with a readily visualized bony structure and the lack of significant breathing-related movement. Repositioning accuracy has been achieved through the use of a body frame with daily CT,[50] fiducial markers implanted into spinous processes,[8,9] combined CT-linac units,[51] or orthogonal x-ray imagers combined with a stereotactic infrared marker array.[52] A variety of fractionation schemes have been used, with doses ranging from 6 to 30 Gy in one to five fractions. Patients have often been treated with SBRT following prior conventional therapy to spinal cord tolerance. Thus, intensity-modulated treatment planning is utilized to minimize dose to the spinal cord while treating the surrounding areas. The spinal cord is a serially arranged organ with respect to radiation injury, and the risk of myelitis is considered insensitive to the volume of cord irradiated. However, recent animal investigations by van der Kogel and colleagues suggest that nonuniform dose distributions (such as produced by intensity modulation) produce a different normal-tissue complication risk compared to uniform distributions, despite an equivalent total volume irradiated.[53] At the commonly accepted cord tolerance dose (45 Gy in 1.8-Gy fractions), the risk of spinal injury is extremely low, and therefore treatment of a large number of patients is required to statistically demonstrate an ability to escalate the dose without increasing the risk of injury.

![Figure 1: Percent Survival of U87MG Human Glioma Cells Following Exposure to Radiation](image) Radiation at 12 or 18 Gy was delivered over the duration of time indicated on the x-axis. Note that for the 18-Gy dose level, increasing the length of treatment from approximately half an hour to 2 hours corresponds to an order of magnitude decrement in cytotoxicity. Adapted, with permission, from Benedict et al.[58]
Optimizing SBRT: Biologic and Physical Strategies and Pitfalls

As it is currently applied in cancer treatment, SBRT is intended to eradicate tumor cells by abolishing their reproductive capacity or inducing apoptotic cell death. This objective is concordant with conventional forms of radiotherapy. However, because SBRT typically involves substantially higher doses of radiation per treatment than conventionally fractionated 3D-CRT, it opens up a broad range of new opportunities for clinical and related translational investigations in an effort to optimize the effectiveness of SBRT.

**Incorporating Traditional Radiosensitizers or Newer Targeted Agents**

Conventional 3D-CRT is often administered concurrently with chemotherapy drugs that primarily impair cancer cell mitosis. The term radiosensitizer is applied loosely in this setting to any agent that augments the clinical efficacy of the radiotherapy, although it may be difficult to determine whether the benefit is derived from additive cytotoxicity or truly synergistic enhancement of radiosensitivity. In fact, as we have discussed elsewhere, the magnitude of any true radiosensitization is highly dependent upon the fraction size in a nonlinear manner, with increasing sensitization as fraction size increases. It has been calculated that in the presence of a true radiosensitizer with even very modest potency, an increase in the daily fraction from 1.8 to 2.2 Gy during a typical 5-week course of radiotherapy will achieve nearly three times more cell killing effect beyond what is produced from the higher dose of radiation alone.[54] In the context of SBRT, with fraction sizes of up to 20 Gy in selected applications, profound radiosensitivity enhancement could be achieved with a true radiosensitizer, because the linear increase in fraction size would correlate with logarithmic increases in the supra-additive effect. However, radiation also triggers a host of defensive responses that potentially counteract the cytotoxic effects, including several conducted through the membrane-bound epidermal growth-factor receptor.[55] The tumor as a whole is protected by reactions that promote cellular repopulation, and individual tumor cells are partially protected as antiapoptotic and DNA repair mechanisms are activated. The cellular signaling events involved in these protective pathways are being studied with the aim of identifying new agents that target and inhibit specific steps and thereby abrogate the cytoprotective effects, but the manipulation of intracellular signal transduction is not necessarily a straightforward process. For example,
radiation-induced activation of the mitogen-activated protein kinase (MAPK) pathway ordinarily serves to compensate for radiation-induced cytotoxicity by promoting cell proliferation and inhibiting apoptosis. The MAPK response increases with increasing radiation doses of up to at least 10 Gy.[56] Typically, SBRT fraction sizes will be at or above this level, in the range expected to cause maximum MAPK pathway activation. It might be intuitively assumed, then, that inhibiting radiation-induced activation of MAPK would convey a consistent radiosensitizing effect. However, there can be paradoxic effects in certain cell types, depending on the sequencing of this intervention with the irradiation. For example, in DU145 human prostate cancer cells, if MAPK signaling is blocked prior to irradiation, then a radioprotective effect is observed. Presumably, a transient cell-cycle arrest at that time allows increased DNA damage repair. On the other hand, blocking the MAPK pathway after irradiation accomplishes radiosensitization by increasing the apoptotic response and reducing clonogenic survival.[ 57] The important implication is that if the use of signal transduction inhibitors is being considered as a way to enhance SBRT, the proper sequencing of these agents within the overall treatment schedule needs to be determined in order to exploit any favorable synergistic effects while avoiding counterproductive interactions.
There are two technical factors that may diminish the biologic efficacy of SBRT—one extrinsic, the other intrinsic. First, there is the potentially detrimental effect of lengthy individual SBRT treatment time. Benedict and colleagues have considered this problem from the perspective of linac-based cranial stereotactic radiosurgery (SRS).[58] These investigators modeled SRS as intermittent irradiation over the range of total times required for multiple-isocenter, multiple-arc treatment delivery—a range of time that overlaps the irradiation time requirements of some systems currently in use for SBRT. Their key observation was that cell survival increased with increasing total irradiation time, presumably a consequence of cellular repair mechanisms that compromise the efficacy of treatment when the duration of an individual fraction is excessively prolonged (Figure 1).[58] Others have also addressed analogous clinical radiotherapy treatment scenarios in which repair processes activated within the time of an individual treatment might diminish the efficacy of the radiotherapy administered. Arnfield and colleagues provided experimental data supporting the concern for a comparable adverse situation if high-dose-rate brachytherapy applications are prolonged,[59] and Welsh and colleagues raised similar apprehensions regarding lengthy individual intensity-modulated radiotherapy treatment times for prostate cancer.[60] In addition to whatever adverse biologic effect would result from prolonging the duration of SBRT, there is another immediate clinical consequence: Patients can become uncomfortable if immobilized for treatment for a lengthy time, often then shifting themselves away from the intended ideal treatment position as they try to relieve muscle cramps or strains. Another well-known problem that complicates SBRT—or any form of external-beam radiotherapy, for that matter—is the presence of hypoxic tumor cells. While tumor volume will have an important effect on projected tumor control probability from a typical SBRT fractionation scheme, even a very low percentage of hypoxic cells will reduce tumor control probability substantially (Figure 2).[61] Once the maximally tolerated dose of SBRT alone has been established for a particular clinical application, yet another avenue for future investigation could include the combination of SBRT and an enhancer of oxygen delivery such as RSR13.[62]
multiple static beams with apertures smaller than the target when considered from a "beam's-eye view" perspective.\[3\] They argued that this method of using a so-called negative block margin can achieve a higher dose centrally within the tumor with only modest increases in the dose within the volume of normal tissue just outside the tumor, thus favorably affecting the therapeutic ratio. In a more quantitative assessment of the impact of margin selection upon both tumor and normal tissue dosimetry, Cardinale and colleagues analyzed the impact of varying the margin around the planning target volume for a lung and liver SBRT case.\[63\] For each of the two targets, plans were generated with block margins of -2.5 to 10 mm around the planning target volume. All plans were normalized such that 99% of the planning target volume was covered by the prescription isodose volume. In these particular cases, it was observed that a margin of 0 to 2.5 mm provided the most favorable effect upon the volume of nonplanning target volume normal tissue receiving a high dose (Figure 3).\[63\] Two points should be noted. First, although Cardinale also analyzed normal tissue complication estimates according to the Lyman model methodology, for parallel organs such as liver and lung, mean dose might be a better predictor of functional compromise. Second, the cases studied should not be assumed to be broadly generalizable, but rather, examples that prompt individual practitioners to consider using margins around target margins that would be considered unusual for conventional radiotherapy but might be beneficial in SBRT. **Current Investigations**

Several phase I/II clinical trials of SBRT for liver and lung tumors are under way. The Radiation Therapy Oncology Group (RTOG) is planning a phase II study in patients with early-stage NSCLC based on the phase I experience from Indiana University. The University of Colorado is the coordinating center of a multi-institution phase I/II study of hypofractionated SBRT for liver metastases. The dose escalation started at 36 Gy in three fractions prescribed to the isodose line (70% to 90%) and will be escalated by 6 Gy total dose per cohort, delivered in three fractions within 5 to 10 days. Dose escalation is now ongoing, and no dose-limiting toxicity has been observed as of the time of this writing. A representative dose distribution and dose-volume histogram for planning target volume and normal liver for a subject enrolled in this study is shown in Figure 4. The RTOG is planning a phase I/II trial of SBRT for patients with unresectable primary hepatobiliary cancer and liver metastases. Patients will be stratified by disease (primary or secondary). The starting dose for phase I will be 30 Gy in 10 fractions, and dose per fraction will be increased by 0.5 Gy per dose cohort to a maximum of 50 Gy. In both studies, extrahepatic disease is allowed as long as life expectancy is at least 3 months and there is no evidence of brain metastases. **Conclusions**

Stereotactic body radiation therapy is an attractively noninvasive technique of cancer treatment that is now being carefully studied in the management of a variety of extracranial tumors. Biologic and clinical rationales support its use in both primary and metastatic tumors of lung, liver, and spine. Although there are variations in the techniques of immobilization and repositioning methodologies used at different institutions, reports from numerous centers document good local control rates with few complications. Long-term follow-up is needed to confirm the preliminary results summarized here. SBRT may offer unique opportunities for the incorporation of new radiosensitizers or targeted therapies into clinical radiation oncology, and technical and biologic refinements offer the potential for future improvement in its effectiveness and safety.

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**References:**


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