Stereotactic Body Radiation Therapy for Liver Metastases

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Abstract

The concept and technique of stereotactic body radiation therapy (SBRT) is presented. This focally tumor-ablative radiation approach is delivered in a few fractions of high radiation doses to a limited volume of metastatic disease to the liver. Indications include one to five metastatic lesions with maximum diameters up to 5 cm. While clinical experience is limited with few larger case series, preliminary outcomes with respect to tumor control and normal liver sparing are encouraging. This new treatment modality offers patients an alternate noninvasive treatment modality promising high local tumor control rates.

Concept of Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) is a relatively novel concept in which high doses of radiation are directed focally onto malignant lesions in organ sites other than the brain, including lung, liver, and spine tumors. The concept of SBRT is derived from the experience in treating metastatic lesions in the brain by stereotactic radiosurgery (SRS). In SRS, very high radiation doses are delivered to small brain lesions in a single session, with the intent to ablate all malignant tumor cells in one setting. The success rates of this treatment approach, with local tumor control rates as high as 93.3 %, have made SRS a standard of care for limited metastatic disease to the brain [1–3]. Similar antitumor efficacy should be achievable for metastatic lesions in organs other than the brain, when high radiation doses are comparably confined to a small tumor. In this chapter, an attempt is made to summarize the clinical experience with SBRT for metastases to the liver. The indications, technical considerations, as well as outcomes of SBRT for liver metastases are discussed, including available data of prospectively designed clinical trials.

SBRT as discussed here will largely adhere to the accepted definition in the United States as the

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delivery of high-dose focused radiation in 1–5 fractions onto small malignant lesions. The high-dose aspect of delivery, as well as what constitutes a small lesion, is less clearly defined. High-dose delivery is most often understood as single-fraction doses exceeding 5 Gray (Gy). Small lesions are most often defined as being less than 5 cm in maximum diameter. Focal radiation delivery refers to the ability to deliver tumoricidal radiation doses in a highly conformal manner, so that a target volume delineated in CT, MRI, or PET imaging is exposed to high, tumor-ablative doses of radiation, while steep dose gradients toward normal tissues afford sparing the organ harboring the disease from radiation injury. However, highly precise dose planning also requires similarly accurate dose delivery. Unique to the concept of SBRT is the stipulation of image-guidance in the context of dose delivery. As such, SBRT is currently the only radiation therapy concept for which a target has to be directly or indirectly localized before the radiation dose is delivered.

Liver Metastases: Incidence and Established Treatment Options

The liver is second only to regional lymph nodes as a site for metastatic disease for a variety of primary malignancies [4]. For colorectal cancer, the liver is often the first site of metastatic disease manifestation, with 15–25 % of patients harboring liver metastases at the time of diagnosis [5]. At autopsy, liver metastases are found in 25–50 % of patients who have died from cancer [6]. For patients diagnosed with liver metastases, the life expectancy without treatment is poor at about 5 months [7].

Surgical resection is the standard therapy for solitary or few lesions confined to the liver with favorable survival rates at 5 years of 25–35 % [5]. Unfortunately, 80–90 % of patients diagnosed with metastatic disease to the liver are not resection candidates, either due to the extent of metastatic disease, multiorgan metastatic disease, insufficient functional liver reserve, or general medical condition [4, 5].

Alternate liver-directed treatment options for patients with limited but unresectable liver metastases include radiofrequency ablation (RFA) [8], transarterial embolization (TAE) with or without transarterial chemotherapy administration (TACE), and radioembolization [6, 7, 9, 10] (Fig. 30.1). Local tumor control rates for RFA are comparable with surgery for lesions less than 3 cm, but lesions in close proximity to large vessels and the diaphragm, as well as subcapsular location, can be relative contraindications for this technique. Cryotherapy has been largely used in the past for palliation of unresectable liver tumors, but high local recurrence rates and peculiar systemic complications have determined its progressive abandonment. Despite long-term clinical use, the optimum number of freeze-thaw cycles, the role of inflow occlusion, and the potential corrupting effects of intralesional or proximal blood vessels on ablation morphology are still controversial [11].

For patients with multifocal liver metastases that are not candidates for liver-directed therapy, chemotherapy represents the only viable treatment option. Advances in chemotherapy treatment have been impressive for a variety of tumors. For patients with metastatic colorectal cancer, for example, the median survival has been improved from 10 to 20 months after the introduction of new chemotherapeutic agents and targeted therapies [10]. Unfortunately, these results are not seen for most other malignancies.

Radiation Therapy for Liver Metastases: From Conventional Radiation to SBRT

For decades, radiation therapy has had a limited role in the treatment of hepatic metastases because of the limited tolerance of the liver. The entire liver will not tolerate more than 30–35 Gy of conventionally fractionated radiation. At higher doses, radiation-induced liver disease (RILD) occurs frequently. RILD describes a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes (particularly serum alkaline phosphatase) occurring from

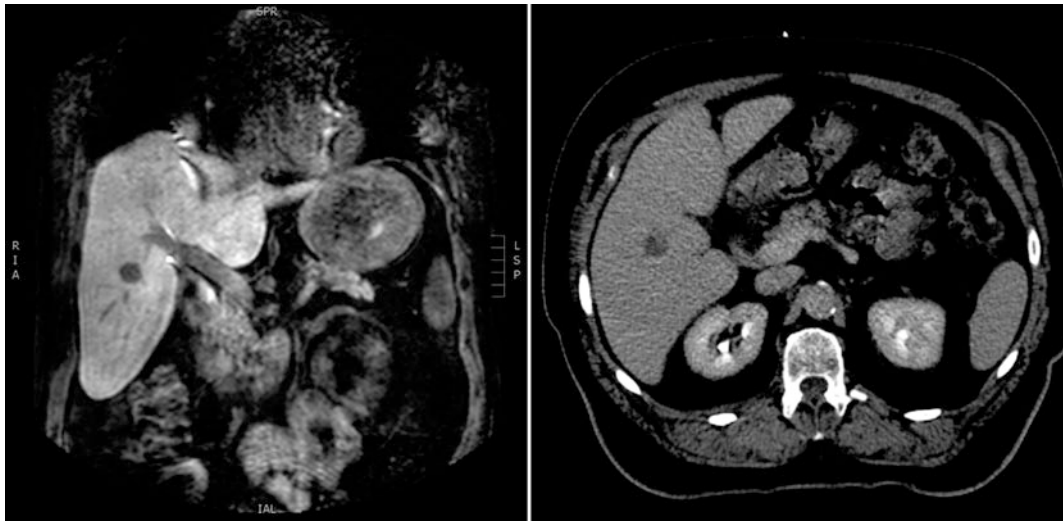

Fig. 30.1 Solitary non-small-cell lung cancer liver metastasis. The lesion is depicted in a coronal reconstruction T1-weighted delayed-phase contrast-enhanced MRI, as well as a delayed-phase post-contrast axial CT. By size (10 mm) and location, this is a candidate lesion for consideration of SBRT. Since at the time of assessment, this lesion represented the only site of systemic disease with locally controlled primary tumor, this could be considered a case of oligometastasis

2 weeks to 3 months following external beam radiation. Diuretics and steroids are often used in therapeutic intent, although evidence is lacking that they change the natural history of RILD. Most cases resolve with conservative, supportive treatment, but some cases lead to irreversible liver failure and occasionally death.

Focal radiation dose delivery to only parts of the liver allows for sufficient normal liver sparing, with an associated lowered risk for chronic liver damage. Recent developments in radiotherapy such as optimized patient immobilization and four-dimensional imaging techniques allow radiation oncologists to assess liver organ motion. Also, three-dimensional treatment planning, image-guidance, and gated or breath-hold radiation delivery have been critical to the high-precision focal irradiation of liver lesions performed with SBRT [12]. In prospective clinical trials, doses prescribed to focal liver lesions could be escalated to 60 Gy in 6 fractions, using modern radiation treatment techniques [13].

Steep dose gradients between liver lesions and surrounding normal liver tissue are a hallmark of SBRT dose distributions and afford excellent liver sparing. This is accomplished by using multiple radiation beams which are shaped according to the tumor outline and are all centered upon a liver lesion (Fig. 30.2). While each of the radiation beams delivers a small fraction of the cumulative radiation dose, the dose at the target, where all radiation beams intersect, is summed up to high tumoricidal dose levels (Fig. 30.3). Similar dose concentrations can be achieved using arc delivery techniques during which a multi-leaf collimator, or radiation beam-shaping device, continually adjusts the radiation port to the shape of the target from a given beam's eye view. SBRT radiation plans use 7–11 individual radiation beams arranged coplanar or noncoplanar around the target lesion, with little incremental plan quality improvement when the number of radiation ports exceeds nine [14–18].

While conventional radiation therapy protocols that are delivered over multiple weeks are computed with homogeneous dose distributions (which expose all aspects of a clinical target volume (CTV) to the same radiation dose), dose distribution used for SBRT often employs heterogeneous dose planning in which the center of a target volume is intentionally exposed to

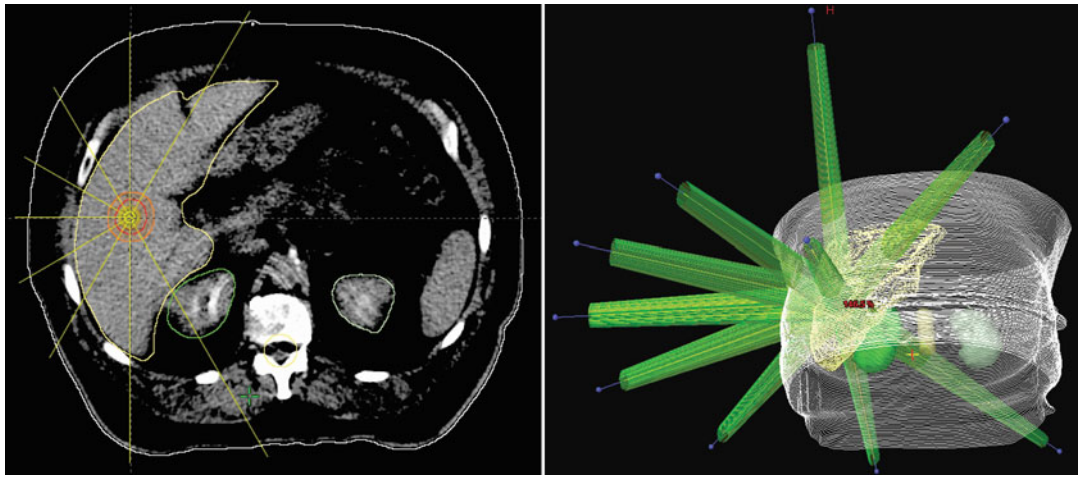

Fig. 30.2 Multi-beam arrangement for SBRT of liver metastases. Here, 10 isocentric beams intersect at the liver metastasis. Each individual beam is shaped to the beam's eye-view outline of the radiation target volume. Eight beams are arranged in a coplanar way, with two additional noncoplanar beams entering from superior anterior and inferior anterior

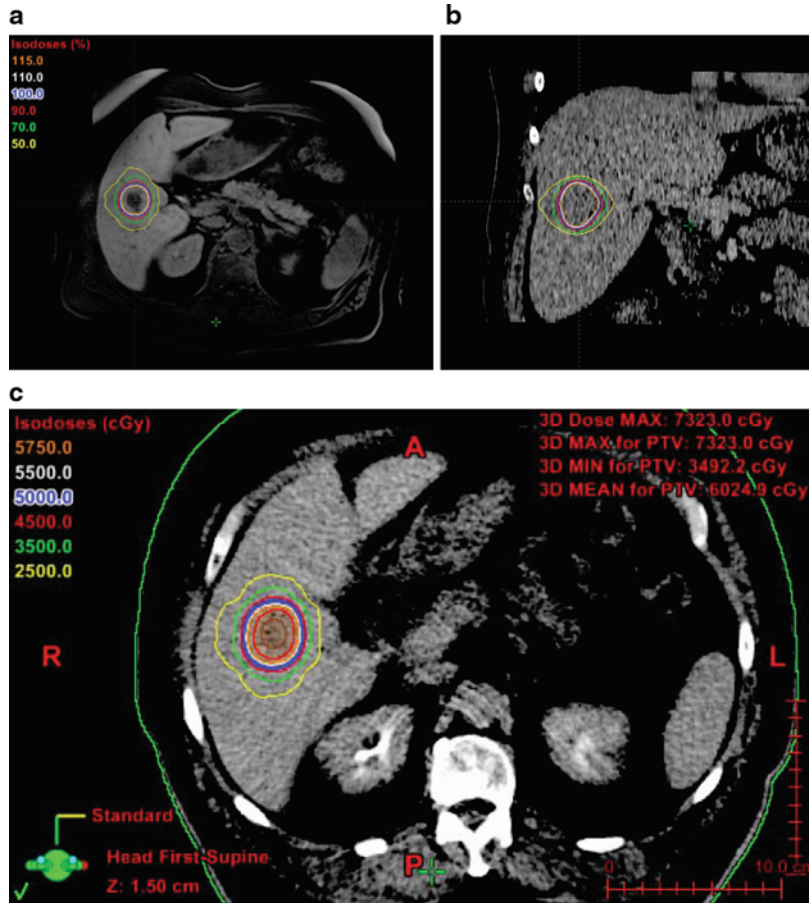

Fig. 30.3 Typical radiation dose distribution for SBRT of liver metastases superimposed onto representative axial and coronal CT slices (**b** and **c**) as well as a co-registered axial MRI (**a**). The *blue, red, green*, and *yellow* lines represent the 50 Gy (100 % of prescribed dose), 45 Gy (90 %), 35 Gy (70 %), and 25 Gy (50 %) radiation dose. Note the steep radiation dose fall off toward the surrounding normal liver, resulting in highly effective healthy liver sparing

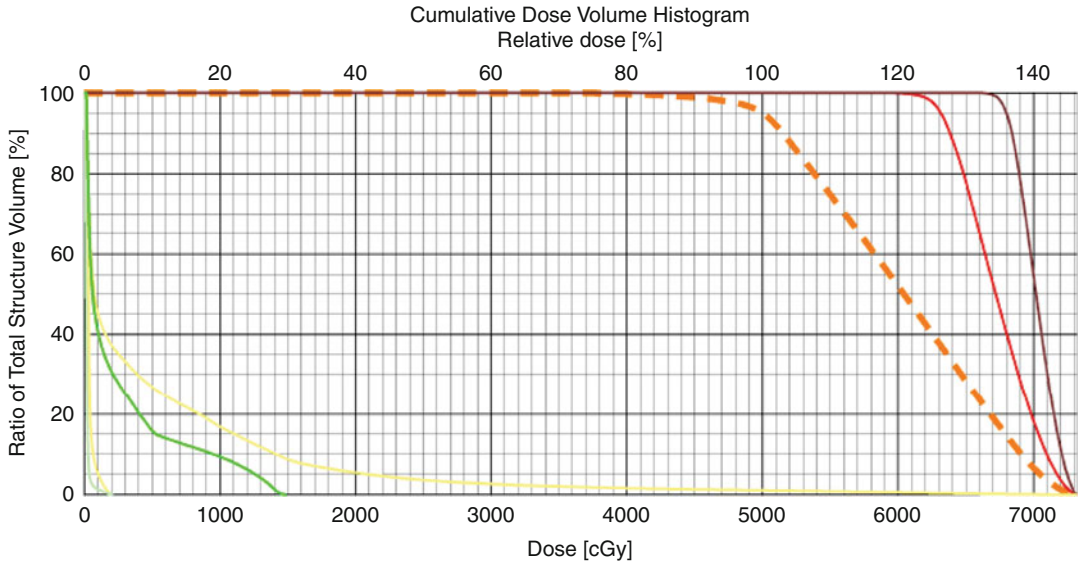

Fig. 30.4 Dose volume histogram (DVH) for SBRT planning of liver metastases. The *orange line* represents the planning target volume (PTV) to which a radiation dose of 50 Gy in 5 fractions is prescribed (95 % of the PTV is exposed to 50 Gy or more). The *red* and *brown* lines represent the target volume and an area delineated for heterogeneous radiation dose prescription. The *yellow* and *green* lines represent liver and right kidney, respectively, with less than 20 % of either organ exposed to more than 20 % of the prescribed dose

25–50 % higher doses than the edge of the target volume [19, 20] (Figs. 30.3 and 30.4). Such heterogeneous dose distributions afford the delivery of higher radiation doses to central tumor aspects that may be hypoxic and protect malignant cells from radiation injury, potentially increasing the clinical efficacy of SBRT [21].

Most SBRT treatments in the US are delivered in 3–5 fraction schedules, with dose delivery every other day or in even lesser numbers of fractions/week [18, 22, 23]. This is in contrast to some European sites pursuing single-dose SBRT for primary and metastatic liver tumors [24–27]. At this point in time, optimal dose scheduling has not been established, and single-dose delivery may result in comparable outcomes to hypofractionated SBRT schedules.

Indications for SBRT of Liver Metastases

Similar to indications for surgery, and other liver-directed therapy options for liver metastases, indications for SBRT include solitary or a low number (<5) of liver lesions. Ideal candidates have metastatic disease limited to the liver or liver lesions considered most life-limiting in the setting of multiorgan systemic disease. Interesting in establishing an indication for SBRT of liver metastases is the concept of oligometastases. The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum as a transitional state between localized and widespread systemic disease [28]. Oligometastatic disease has the potential of progressing to widespread metastatic disease. Thus, local control of oligometastases may yield improved systemic control [29, 30]. While indications for SBRT overlap with many other treatment modalities, there are distinct exceptions which deserve discussion. Primarily, there is no strict size limitation for the use of radiation therapy. While an upper size limit of a liver metastasis of 5 cm is defined in most prospective clinical trials for eligibility of SBRT, larger lesions could be treated using the exact planning techniques and technology used to deliver SBRT [12, 24, 26]. The challenge in treating larger lesions with SBRT techniques is

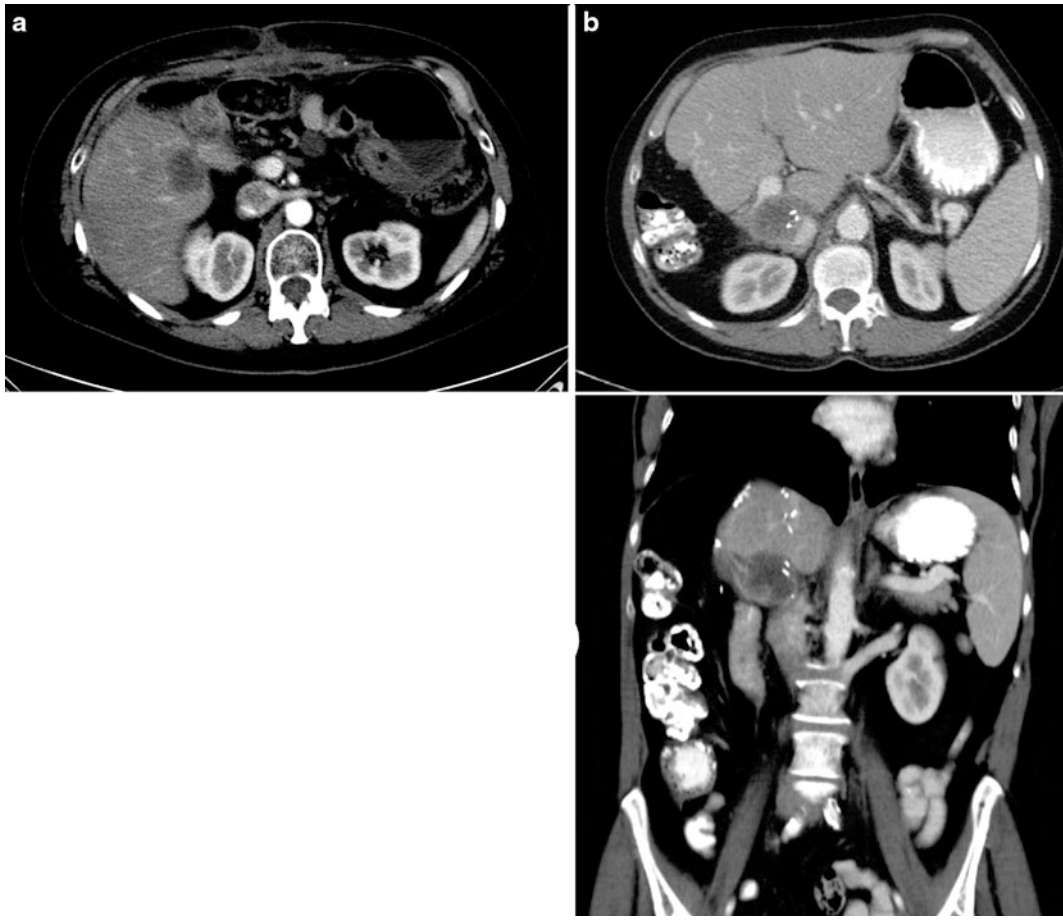

Fig. 30.5 Contraindication for SBRT of liver tumors. While subcapsular location in itself does not represent a contraindication for SBRT, proximity to hollow organs such as stomach or small and large bowel does. Figures (**a**) and (**b**) represent two cases in which a lesion (*arrows*) which is suitable by size for SBRT is located close to bowel loops. Note that the axial slice in figure B does not indicate the close proximity of a resection margin recurrence of metastatic colon cancer to a small bowel loop as well; this becomes more evident in coronal CT reconstruction

the sparing of normal liver volume and avoidance of exposing bowel or other lesion to potentially harmful radiation levels. These limitations often force lowering radiation dose prescription for treatment of large liver metastases, with subsequent lowered tumor control probability. Lesion location within the liver may be less critical for SBRT treatment than for alternate modalities such as RFA or cryoablation. Specifically subcapsular and subdiaphragmatic lesion locations in close proximity to large blood vessels and central lesion location are not definitive contraindications to SBRT. The key consideration when evaluating patients for an indication for SBRT is the proximity of the lesion to hollow organs such as the colon, stomach, or the duodenum (Fig. 30.5). If maximum radiation dose exposure to an aspect of those organs exceeds safe dose limits, SBRT would be contraindicated and radiation therapy may be denied or a more conventionally fractionated treatment course may be recommended. The second most important consideration is residual normal liver volume and underlying liver function. Most prospective clinical trials stipulate a minimum non-tumor liver volume of

700–1,000 cm^3 and reasonable baseline liver function (total bilirubin less than 3 mg/dL, albumin greater than 2.5 g/dL, and normal prothrombin/partial thromboplastin times (unless on anticoagulants) and serum liver enzymes less than three times the upper limit of normal) [22, 23].

SBRT for Liver Metastases: Challenges and Technical Considerations

Owing to the higher tumor-ablative doses delivered with SBRT, knowledge about the target's location and assurance that the patient will not move during radiation dose delivery are critical components of the safe integration of SBRT into the management of liver metastases. It is critical that the SBRT dose is actually delivered onto the target lesion and not accidentally into normal tissues. These challenges can be addressed at least partially by immobilizing the patient's body, preferably by use of whole-body immobilization devices [31–34]. However, while immobilization of the patient's body will locate a target volume close to a predicted treatment position relative to the linear accelerator radiation beam geometry, tumors in the liver can move relative to the bony skeleton rendering an assessment of the patient's position by bony X-ray analysis unreliable [24, 31, 35–38].

Image-guidance, a stipulated component of SBRT delivery in the US, can be used to assess the position of a liver target either by direct visualization or indirectly by assessing the position of the liver or liver lobe harboring the target through radio-opaque fiducials implanted within close proximity to the liver metastases. The obvious challenge here is that liver metastases may or may not be visualized on non-contrast imaging. If an imaging modality other than a diagnostic grade CT scanner is used for image-guidance, such as megavoltage port films, kilovoltage X-ray-based images, or on-board cone-beam CT (CBCT) units, the liver soft tissue contrast will likely be insufficient to depict a liver lesion. The only alternate modality capable of rendering soft tissue structures in the liver is ultrasound. Consequently, two-dimensional ultrasound-based image-guidance has been successfully implemented into the image-guidance workflow for SBRT at select institutions [39].

Liver motion due to breathing during treatment simulation and delivery can be substantial. In order to treat small liver lesions with a focal radiation approach, liver tumor motion must be accounted for to ensure proper delivery of the radiation dose to the tumor and to avoid unnecessary dose exposure of normal tissues. Further complicating this issue is the observation that substantial variations in breathing motion are seen among patients, with motion amplitudes ranging from 5 to 35 mm. Motion occurs predominantly in the cranio-caudal direction, followed by the anterior-posterior direction [40, 41]. In order to account for liver motion during respiration, several approaches can be chosen. The most conventional measure is the addition of so-called planning target volume (PTV) safety margins on a defined liver target volume. The creation of a PTV extends the target volume by adding between 5- and 10-mm margins into the surrounding normal tissues. To develop individual PTV margins, the organ motion during respiration needs to be measured by acquiring imaging studies during inhalation and exhalation or by using fluoroscopy. Other approaches employ means to restrict organ motion such as exerting pressure upon the upper abdomen or using breath-hold imaging and delivery techniques. All of these measures aim at minimizing PTV margins which are exclusively comprised of normal tissues at risk for radiation-induced damage [38].

More recently, it has become possible to define organ motion based on so-called four-dimensional CT (4DCT) studies by sorting an oversampled CT image dataset into phases of a breathing cycle. Delineating a target in all phases of the breathing cycle allows deriving an internal target volume (ITV). An ITV is representative of the motion envelope containing the tumor at all times during the breathing cycle. Use of a 4DCT for SBRT planning also allows identifying the subset of a breathing cycle during which a target volume or the liver moves only to a smaller degree. The concept of gating uses

this information and will enable radiation beam delivery only when the liver and thus the target are in a defined proportion of the breathing cycle [42]. Such a technique minimizes the volume of an ITV and also the additional liver volume included in a PTV [43, 44]. A major drawback to this technique is a prolongation of treatment delivery, as often up to 70 % of the potential beam delivery time is disabled [45]. Thus, overall treatment times may be prolonged by up to three times over non-gated delivery. Additional concern exists regarding the reliability of 4DCT-based SBRT planning. Both ITV-based planning concept and gated treatment delivery assume a reproducible amount of organ motion during respiration to afford PTV margin reduction. However, in a worst-case scenario, margins may need to be increased to accommodate inter-fraction variations in respiration [46].

Breath-hold planning and delivery techniques require patient compliance, but do not prolong overall treatment delivery when the patient can hold their breath for reasonable amounts of time. Typical patients can hold their breath for 20–35 s, which is sufficient to deliver a respective radiation field from a given gantry angle [47–49]. For rotational radiation administration, the beam delivery needs to be interrupted, and the arc broken into shorter arc segments according to the patient's ability to hold their breath. The adaptation of the treatment planning and delivery process for breath-hold must be done with caution. First, the reproducibility of the breath-hold must be established on a patient specific basis. Not all patients are suitable candidates for breath-hold; for some patients, the target positional variation resulting from various breath-hold maneuvers within the same treatment session is as large as the breathing motion [50].

Real-time tumor tracking during radiation treatment delivery is another approach to reduce adverse effects of organ motion. Motion tracking is driven by the correlation between the location of fiducial markers near the tumor, as detected in orthogonal X-rays, and the location of external markers on the patient's chest. The correlation model is built just after patient setup and is updated throughout the treatment session each time verification X-rays are obtained. Several technical solutions to tumor tracking are realized or subject to ongoing research, including moving the entire linear accelerator, continuous adjustment of the couch position, or use of the multileaf collimator (MLC) to track the shape of a lesion as it moves with respiration [51–55].

Clinical Experience with SBRT of Liver Metastases: Early Institutional Experience

In 1995, Blomgren and Lax published the results of a landmark pilot study researching the potential to establish the use of extracranial stereotactic radiotherapy [56]. The pilot study included patients with primary liver tumors, as well as liver metastases and reported outcomes after 20–45 Gy in 1–4 fractions. In 9 patients, 12 tumors ranging from 5 to 622 cm^3 were treated. Complete response was observed early in follow-up for small tumors (Fig. 30.6 depicts a comparable case), but the time to maximal response was prolonged for larger tumors. In 1998, the Karolinska group updated the data after a median follow-up of 9.6 months for 17 patients with liver metastases. Stable disease was seen in 10 tumors, partial response in 4, and the local control rate was 95 % with a mean survival of 17.8 months [26].

The University of Heidelberg group reported outcomes on 60 liver tumors including 56 metastases in 37 patients treated in a phase 1 dose escalation study [24] . Median target volume was 10 cm^3, with a range from 1 to 130 cm^3. Single-dose delivery was escalated from 14 to 26 Gy. At the 26 Gy dose level, further dose escalation was stopped, despite the fact that a maximally tolerated dose (MTD) was not established. There were no major side effects. Eleven patients experienced an intermittent loss of appetite or mild nausea for 1–3 weeks after therapy. Two patients with tumors close to the diaphragm experienced moderate singultus for 2–3 days after therapy. One patient developed fever lasting for 2 days after therapy. None of the treated patients developed clinically

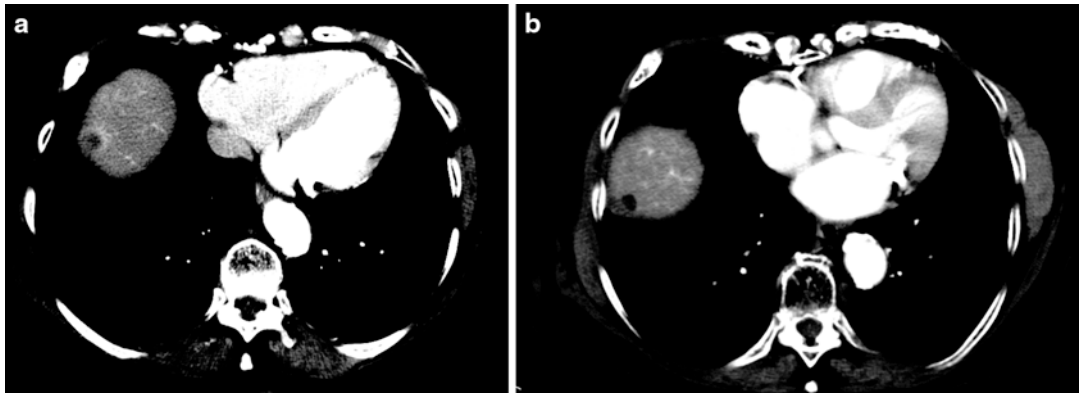

Fig. 30.6 Endometrial cancer liver metastasis before (**a**) and 9 months after SBRT (**b**). Note the loss of rim contrast enhancement in post contrast arterial phase CT scans. A cyst-like remnant can be observed after SBRT

detectable radiation-induced liver disease. Fifty-four (98 %) of 55 tumors were locally controlled after 6 weeks at the initial follow-up based on the CT findings with 22 cases of stable disease, 28 partial responses, and 4 complete responses. The actuarial local tumor control rate was 81 % at 18 months after therapy. A total of 12 local failures were observed during follow-up.

Investigators from the University of Wuerzburg in Germany included 39 patients with 51 hepatic metastases into a prospective study of single- and multi-fraction SBRT [12, 57]. Actual doses prescribed were 30 Gy in 3 fractions (n = 24) and 28 Gy in 4 fractions (n = 1) in a total of 25 lesions, and these patients were analyzed as a low-dose cohort. Patients considered in a high-dose cohort received doses of 37.5 Gy in 3 fractions (n = 13) or 26 Gy in a single setting (n = 8). Mean clinical target volume was 83 cm^3. At a median follow-up of 15 months, nine local failures were observed. Actuarial tumor control was 92 % and 66 % at 1 and 2 years. Eight local recurrences were observed in the low-dose group, with 50 % of colorectal liver metastases in this group experiencing local failure. In 11 colorectal cancer metastases in the high-dose group, no local failure was documented. Consequently, local tumor control was higher in the high-dose group with 100 % and 82 % at 1 and 2 years than in the low-dose group with 86 % and 58 % local control rate at 1 and 2 years. No acute grade 3–5 side effects were observed. Also, no late toxicity clearly related to radiation was documented. Overall survival was 71 % and 41 % at 1 and 2 years.

These landmark series have provided encouraging early outcomes for SBRT treatment of liver metastases. Since the early inception in Sweden, and Germany in the 1990s, additional institutional data and retrospective series analyses have become available.

At Erasmus University, 17 patients with 34 metastatic liver tumors were treated in a phase 1–2 institutional trial to doses of 30–37.5 Gy in 3 fractions [58]. All but 3 patients were diagnosed with metastatic colorectal cancer, and the liver was the only site of metastases at time of treatment. Liver metastases ranged from 0.5 to 6.2 in maximum diameter, and up to 4 lesions were treated. The dose was prescribed to the 65 % isodose surrounding the PTV, resulting in a dose maximum of 150 % at the center of the lesions. For the patients with metastases, the 1- and 2-year actuarial local control rates were 100 % and 86 %, respectively. Local relapse was observed in two metastases after initial complete remission. Overall survival was reported as 85 % and 62 % at 1 and 2 years, respectively. Grade 3 toxicity was observed in two patients with elevation of gamma-glutamyltransferase, potentially related to exposure of 47 % and 40 % of normal liver to doses higher than 15 Gy. This relatively high exposure of the normal liver was a consequence of treating 2 lesions

simultaneously in one patient and presence of a small, post-resection liver volume in the second patient. One case of grade 3 asthenia was observed in a patient who was treated with chemotherapy and resection prior to SBRT. In a 2010 update including at least some of the above-summarized patient population, but with longer follow-up, the 1-year local control rate remained at 100 %, but the 2-year local control (defined as an increase in size based on contrast-enhanced CT or MRI studies) was reduced to 74 % [59]. At a median and maximum follow-up of 26 and 57 months, 9 of 20 patients analyzed had died. Median survival was 34 months, with 2-year survival of 83 %. The same group of investigators studied quality of life following SBRT for liver lesions, including 19 patients with 38 liver metastases [60]. While data were not reported and stratified by primary versus secondary liver lesions, quality of life was maintained for 6 months in patients with continued local tumor control. This finding provided the rationale for further research in a larger multi-institutional study in Europe.

In a recently published phase I study from the Princess Margaret Hospital in Toronto, 68 patients with colorectal cancer liver metastases were treated in a 6-fraction SBRT regimen [13]. Eligible patients had exhausted or were refractory to standard treatment. If extrahepatic systemic disease was present, the largest disease burden had to be hepatic. Individualized radiation dose prescription was based on estimated risk levels for development of RILD and ranged between 27.7 Gy and 60 Gy. The median SBRT dose was 41.8 Gy delivered over 2 weeks. Overall, the investigators found this treatment to be well tolerated, with no acute/subacute RILD, other serious liver toxicity, or any dose-limiting toxicity observed. However, in longer follow-up, one duodenal bleeding event was observed in a patient with progression and invasion of a treated liver metastasis into the organ and another case of delayed small bowel obstruction. Two patients experienced nontraumatic rib fractures, potentially related to chest wall radiation exposure. Tumor response was observed in 49 % of cases with predominantly partial tumor responses or disease stabilization. Complete tumor response was rare and only observed in 4 cases. Median time to maximum response was 6.2 months, and the 1-year local control rate was 71 %. Local control was improved in smaller tumor volumes and in patients that received higher radiation doses. Based on these pilot data, a phase II trial from these investigators is currently underway.

Investigators from the University of Rochester summarized the outcomes of 69 patients with 174 liver metastases treated by a 10-fraction hypofractionated radiation regimen to a total dose of 50 Gy. While this dose delivery schedule would not be considered under the SBRT paradigm, dose planning and delivery techniques match all aspects of typical SBRT. As such, this large retrospective series is included in this review. Dose was prescribed to the 100 % isodose line (IDL), with the 80 % IDL covering the gross tumor volume with a minimum margin of 7 mm. The median overall survival time in this series was 14.5 months, and the actuarial in-field local control rates were 76 % and 57 % at 10 and 20 months, respectively. Complete responses were rare and only observed in five patients. The majority of patients showed partial response ($n = 15$) or stable disease ($n = 33$). In-field recurrence after initial response or disease stabilization was observed in five patients, with median time to relapse of 6.6 months. The limitations of any focal treatment regimen for liver metastases are highlighted by the fact that in 75 % of patients, new hepatic disease manifests during follow-up. The progression-free survival rates were 46 % and 24 % at 6 and 12 months, respectively. While grade 1 or 2 liver function test elevations were noted in 28 % of patients, no grade 3 or higher hepatic toxicity was observed [23].

Prospective Multicenter and Cooperative Group Clinical Trials

The Aarhus University group published results of a multi-institutional phase 2 study on SBRT for colorectal cancer metastases [27]. The study

enrolled 46 patients for treatment of liver metastases between 1999 and 2003. While initial patient enrollment was limited to liver-only metastatic disease, patients were also accepted later when no more than two organ sites (none of them necessarily the liver) were involved in systemic disease. Total dose was 45 Gy in 3 fractions prescribed to the isocenter, with the edge of the PTV receiving no less than 67 % of the prescribed dose (roughly 10 Gy × 3). Outcomes were not reported for lesions by organ site, and enrollment included approximately 30 % of patients with non-hepatic lesion location. Median time to progression was 6.5 months, with most patients developing distant failures or new lesions in the same organ. Median survival was 1.6 years. Hepatic metastases inferred a poorer survival than extrahepatic systemic disease. While one death and three serious adverse events (colonic and duodenal ulcerations) were recorded, the overall morbidity associated with SBRT was considered moderate.

In a multicenter phase I/II clinical trial led by investigators at the University of Colorado and Indiana University, 18 patients with liver metastases were treated on an initial phase I dose escalation protocol; an additional 29 patients were subsequently enrolled in the phase II component of the study [22, 61, 62]. Eligible patients had one to three hepatic metastases, with maximum individual lesion diameter less than 6 cm. In the phase I study, radiation doses were escalated from 36 to 60 Gy in 3 fractions; all patients in phase II were treated to 60 Gy. The dose was prescribed to the 80–90 % isodose (equivalent to 80–90 % of prescribed dose), and at least 700 cm^3 of normal liver had to receive a total dose less than 15 Gy. Results of the phase I component of the study indicated that doses of up to 60 Gy in 3 fraction regimens could be delivered safely for hepatic metastases [23]. While the maximum tolerated dose was not reached, the study successfully enrolled at the highest predefined dose level. The primary phase II study endpoint was in-field tumor control. At a median follow-up of 16 months, local progression was observed in only three of 49 assessable lesions [62]. Median time to progression was 7.5 months after SBRT. Actuarial in-field local control rates at 1 and 2 years after SBRT were 95 % and 92 %, respectively. Among lesions with maximal diameter of 3 cm or less, 2-year local control was 100 %. Median survival was 20.5 months, although 45 % of the patients had active extrahepatic disease at the time of treatment.

In summary, the published results on SBRT of liver metastases are encouraging with respect to offering patients an alternate noninvasive treatment modality promising high local tumor control rates. However, the range of different doses and fractionation schedules used demonstrates the current lack of a consensus regarding the optimal SBRT protocol for liver metastases. Further studies are necessary to define the ideal dose fractionation schedule to achieve optimal tumor control with minimal side effects.

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