18 Stereotactic Body Radiation Therapy for Liver Metastases: Radiation Therapy Planning

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18.1 Introduction

- Stereotactic body radiation therapy (SBRT) offers a novel, noninvasive definitive local therapy for metastatic liver disease.
- With advances in target localization, tumor motion control, and radiation planning systems, SBRT has become a highly conformal, ablative, and relatively safe treatment modality for these tumors.
- The parallel arrangement of functional subunits in the liver provides some protection against ablative doses of radiation, as long as an adequate proportion of the normally functioning liver is preserved.
- Early clinical data has been promising, with local control rates exceeding 90 %.
- This chapter will discuss SBRT contouring and treatment planning for metastatic liver lesions.

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18.2 Overview of Stereotactic Body Radiation Therapy

- SBRT relies on three fundamental principles [1]:
  1. Precise, reproducible stereotactic localization of the tumor (either using internal or external references)
  2. Daily image guidance for tumor relocalization as well as visualization of critical normal organs
  3. Treatment delivery in one to five fractions
- Integration of SBRT into the management of liver metastases can only be accomplished with sophisticated treatment planning systems, tumor motion control, and localization techniques to allow for accurate and consistent targeting of the tumor.
- These allow for ablative tumor doses while minimizing toxicity to critical organs at risk including the uninvolved liver parenchyma, the chest wall, and the gastrointestinal tract.
- Now several prospective trials use single-fraction versus multifraction SBRT for liver metastasis.
  - The majority of these trials treated 1–5 liver metastases, with tumors measuring no greater than 6 cm in largest diameter. The trials included patients with both favorable and unfavorable prognoses [2].

T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_18

  - Most metastatic liver lesions were from colorectal cancer.
  - Overall, 1- and 2-year local control rates ranged from 70 to 100 % and 60 to 90 %, respectively.
- Fractionated SBRT allows for delivery of highly conformal treatment of targets that are in close proximity to critical structures.
- Fractionation has been hypothesized to improve the therapeutic ratio, thereby reducing the risk of late complications potentially associated with a large single dose [3].
- Radiobiologically, the higher dose per fraction with SBRT-based treatments has been shown to provide improved local control over standard fractionation [4].

18.2.1 Patient Selection

- Patients eligible for SBRT treatment to the liver should be discussed in a multidisciplinary fashion.
- Cases that may be resectable and who have adequate hepatic function should be reviewed with the surgeon.
- Based on data from current prospective trials treating liver lesions with SBRT, patients considered for SBRT should typically have five or fewer lesions with a size of no more than 6 cm in maximum diameter [5].
- Adequate baseline liver function and sufficient uninvolved liver volume which can be spared should be established prior to treatment.
- Tumors which are in close proximity to adjacent radiosensitive structures, such as those close to the hilum, can potentially be treated with SBRT, but the total dose and fractionation scheme may need to be adjusted to meet the dose constraints of the adjacent organs.
- Outside of current published studies, SBRT to lesions that are large (>6 cm) or patients who present with multiple lesions need to be considered on a case by case basis.

18.3 Image-Guided Radiation Therapy (IGRT)

- Lars Leksell [6] developed the first frame-based radiosurgery technique called Gamma Knife® (Eklekta AB, Stockholm, Sweden), which was utilized to treat intracranial disease.
- Subsequently, Blomgren and colleagues [7] utilized a frame-based technique encompassing the head down to the thigh, enabling stereotactic delivery of high-dose radiotherapy to liver and lung lesions.
- Early experience with SBRT for liver lesions was based on the use of a stereotactic body frame to coordinate points in a patient with points in stereotactic space.
- With improvements in onboard imaging, the use of image-guided radiotherapy has superseded the need for the stereotactic frame.
- The patient setup process has changed significantly over the last 10 years, and most institutions are using more standard molds for patient immobilization.
- With the reliance on image guidance during delivery of radiotherapy, there is a greater need for accurate target localization.
- As opposed to lung lesions, visualization of tumors in the liver is limited based on non-contrast cone beam CT scan.
- Fiducial markers should be placed prior to the simulation process to allow for accurate identification of the target and to assess the motion of the target to account for respiratory motion using techniques that will be described later.
  - Gold fiducials are often placed percutaneously into or around the liver lesion to assist in target identification [8].
  - At least two to three fiducial markers are necessary to triangulate where the tumor is located and for tumor tracking during treatment.
  - Postoperative clips can also sometimes be used to localize the treatment target.

- Most new linear accelerators can obtain higher-quality diagnostic x-rays and have onboard three-dimensional (3D) CT imaging, known as cone beam CT (CBCT).
- This provides real-time assessment of tumor positioning while the patient is lying on the treatment table.
- Image-guided radiation therapy (IGRT) has significantly advanced the radiation oncology field, allowing for better target alignment which is critical when treating with SBRT to organs such as the liver, as there is substantial degree of inter- and intra-fraction variability.

18.4 Motion Management

- Smaller fields required for SBRT may miss the liver target if tumor motion with respiration is unaccounted for.
- Studies have shown that the liver can move as much as 1–8 cm in the superior-inferior direction and to a much lesser degree from anterior-posterior with respiration [9].
- Variation in hollow organ filling due to gastric contents may also contribute to both inter- and intra-fraction motion.
- Due to significant liver motion, alignment to bony landmarks is not optimal.
- IGRT, combined with motion management, is therefore frequently utilized for liver SBRT.
- Motion management incorporated in the radiation oncology clinic today can broadly be categorized as motion compensating or motion restricting [8].

18.4.1 Motion-Compensating Techniques

- Respiratory gating relies on delivery of radiation at specific phases of the breathing cycle, usually during the expiratory phase where motion is the smallest.
  - To allow for the linear accelerator to trigger the beam on time, there are several systems available which use external body markers to track the patient's respiratory cycle.
  - RPM system (Varian Medical Systems, Palo Alto, CA) uses external infrared-emitting markers placed on the patients' chest or abdominal wall and can be tracked by an infrared camera.
  - Chest wall motion throughout the respiratory cycle can be recorded, and at a particular height of the fiducial (amplitude-based gating), the system will activate radiation beam on time during the appropriate cycles of respiration.
  - External fiducial movement can be approximated to the breathing cycle, triggering beam on during particular phases of respiration, known as phase-based gating.
  - These forms of respiratory gating correlate with chest wall motion, which does not necessarily correlate with the motion of internal organs including the liver.
  - One option is to take intra-fraction kilovoltage imaging of the target and use the gold fiducials that were placed in or around the liver tumor to confirm in real time that the fiducial markers are moving into the appropriate position when the beam is on.
  - Fluoroscopy can be used prior to treatment to evaluate the excursion of the fiducial markers.
- Tumor tracking using the CyberKnife® system utilizes fiducial markers to localize the tumor [10, 11] and can track tumors in real time.

18.4.2 Motion-Restricting Techniques

- Abdominal compression
  - Abdominal compression uses a belt that compresses the abdominal cavity, increasing intra-abdominal pressure and limiting diaphragmatic respiratory motion, which

translates to decreased liver motion during respiration.
  - Abdominal compression can reduce superior-inferior tumor motion by as much as 50 % [12].
- Active breathing control (ABC)
  - Deliver treatment while a patient holds his or her breath during a specific phase of the breathing cycle.
  - This requires patient instruction on proper respiration patterns in addition to video tracking to deliver radiation at indicated points of the breathing cycle.
  - Dawson and colleagues [13] reviewed patients undergoing SBRT for unresectable liver cancers immobilized with ABC. They found that absolute systemic errors were reduced from 4.1 to 1.1 mm superior-inferior, from 2.4 mm to 1.3 mm anterior-posterior, and from 3.1 to 1.6 mm medial-lateral.

18.5 Patient Setup and Simulation

- The simulation process for SBRT should be done at least 3–5 days after placement of the fiducial markers to minimize any potential changes due to local inflammation or migration of the fiducial marker after the planning process.
- Simulation typically includes a computerized tomography (CT) simulation with intravenous (IV) contrast.
- Many institutions now employ four-dimensional (4D) CT to better delineate the motion of the liver lesion.
  - 4DCT is acquired using a modified CT scanning technique that is synchronized with the respiratory pattern of the patient.
  - The respiratory cycle of a patient is divided into numerous breathing phases, with end inspiration, end expiration, and interval phases between inspiration and expiration.
  - For each breathing phase, a three-dimensional construction is created, and these imaging sets at different breathing phases are constructed and analyzed to determine organ positions at all phases of respiration.
- Most patients will also have a diagnostic multiphasic contrast-enhanced helical CT scan to assist in target localization.
- For liver tumors in particular, CT scans alone may not clearly delineate disease.
- Therefore, incorporation of a fluorodeoxyglucose positron emission tomography (FDG-PET) scan and magnetic resonance imaging (MRI) during planning can be helpful in better identifying the target.

18.6 Target Definition and Dose Prescription

- Gross tumor volume (GTV) encompasses disease delineated by the simulation CT acquired and additional imaging including MRI and PET/CT.
- Internal tumor volume (ITV): If there is 4DCT capability, an ITV, which encompasses the entire motion of the tumor during respiration, can be contoured to create patient-specific margin expansions.
- Planning tumor volume (PTV) depends on the type of motion management approach and can range from 3 to 5 mm in cases where devices are available for real-time tracking of respiratory motion to larger margins of 5–10 mm in the presence of motion compensation techniques.
- Total dose of radiation is typically prescribed to the isodose lines that encompass the PTV.
- From the current prospective SBRT liver trials, there is substantial variability with the prescription dose covering anywhere from the 65 to 90 % isodose line [14–17].
- General dose recommendations range from 18 to 30 Gy in one fraction and 30 to 60 Gy in two to five fractions.

- Fairly standard fractionation schemes based on current literature include 20 Gy × 3 and 15 Gy × 5 for tumors adjacent structures such as bowel or central bile ducts.
- Central tumors near the liver hilum may need to be treated to lower doses or a higher number of fractions due to the proximity to critical structures [16].

18.7 Treatment Planning and Delivery

18.7.1 Intensity-Modulated Radiation Therapy (IMRT)

- Treatment plans undergo automated optimization using intensity-modulated radiation therapy (IMRT) planning (Fig. 18.1).
- IMRT planning takes into account the prescribed target volume and dose constraints on normal tissue and utilizes a computer-optimized algorithm to deliver radiation to achieve proper dose coverage while maintaining dose-constraint goals.
- The computer software is able to define the high-dose regions covering the tumor and subclinical disease while limiting dose to normal organs based on inputted constraints.
- Volumetric modulated arc therapy (VMAT), a form of IMRT, allows for rapid conformal delivery of radiation with multiple gantry rotations, gantry speeds, and dose rates, with dynamic multileaf collimators (MLC).
- VMAT employs multiple coplanar and noncoplanar beams of variable intensity, delivered from many different angles.

18.7.2 Dose Constraints for SBRT Liver Metastases

- Surgical series have demonstrated as much as 80 % of normal liver can be resected without causing liver failure [18, 19].
- Prior to SBRT, radiation had a limited role in ablative treatment of liver metastases due to low whole-liver tolerance with a 5 % risk of radiation-induced liver disease (RILD) with whole-liver doses of 30–35 Gy in 2 Gy per fraction [20, 21].
  - RILD syndrome is characterized by anicteric ascites with elevated alkaline phosphatase and liver transaminases, which typically occurs several weeks to months after radiation therapy.
  - RILD can lead to liver failure and death.

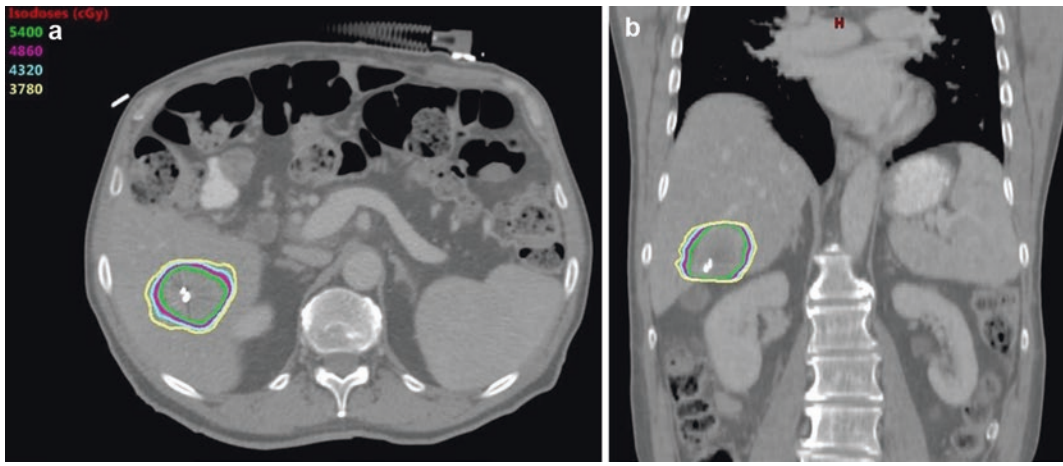

Fig. 18.1 Patient with oligometastatic pancreatic cancer with an enlarging right hepatic lobe segment 6 lesion measuring 1.8 cm, treated with stereotactic body radiation, 54 Gy in three fractions. Axial (**a**) and coronal (**b**) computerized tomography imaging illustrating the final treatment plan

18.8 Potential Toxicities from Treatment

18.8.1 Hepatotoxicity

- Most commonly utilized dose-tolerance model used in SBRT for normal parenchyma is that at least 700 mL of normal liver receive <15 Gy of total dose.
  - Model was first introduced by Schefter and colleagues [15] in a phase I dose-escalation trial for hepatic metastases.
  - In this study, dose was escalated from 36 Gy to 60 Gy in three fractions, and a "critical volume" model requiring at least 700 ml of normal receive <15 Gy of total dose was implemented.
  - There was no grade 3 or higher hepatotoxicity reported.
  - Currently, there are no reported prospective dose-escalation trials that have reached a maximum-tolerated dose (MTD) for hepatotoxicity [14–17, 22, 23].
- The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) therefore suggest ≥700 mL of normal liver receives ≤15 Gy in three to five fractions [24].
- Additional QUANTEC recommendations of mean normal liver dose for SBRT liver metastases include <15 Gy for liver metastases, in three fractions, and <20 Gy for liver metastases, in six fractions.
- Other available liver constraints include limiting the V_{15} and V_{21} to 50 % and 30 %, respectively, for three fractions [25].
- A number of models estimating volume dependence of normal tissue toxicity in liver have been used.
  - The Lyman model was one of the first which assumes a sigmoid relationship between a dose of uniform radiation given to a volume on an organ and the chance of a complication occurring.
  - However, as dose distributions are not uniform, additional calculations needed to be made.
  - Effective liver volume (Veff) irradiated is defined as the normal liver volume minus all GTVs, which if irradiated uniformly to the treatment dose would be associated with the same risk of toxicity or normal tissue complication probability (NTCP) as the nonuniform dose distribution [26].
    - Dawson and colleagues [27] analyzed the risk of RILD in 203 patients followed prospectively after being treated with conformal liver RT, using the Lyman-Kutcher-Burman (LKB) NTCP model.
    - Mean liver dose was 32 Gy, and the majority was treated with partial liver radiation.
    - The lower Veff correlated with significantly lower risks of RILD, demonstrating that in the setting of dose escalation, high doses can be delivered as long as the mean dose to the liver is taken into account.
    - In their analysis, a threshold volume effect was demonstrated with nearly zero incidence of RILD at an effective liver volume of less than one-third.
- Cirrhotic livers are known to have lower tolerances to SBRT [24, 28], and therefore most prospective trials excluded patients with Child-Pugh B classification or higher [15–17, 22].
- Overall, RILD occurs in less than 5 % of all reported SBRT cases.
  - In the phase II SBRT liver metastases study conducted by Méndez-Romero and colleagues [28], there were two cases of RILD, one classic and one nonclassic; an additional patient with hepatocellular carcinoma and baseline Child-Pugh B experienced portal hypertension and nonhepatic infection and died within 2 weeks of treatment.
  - Hoyer and colleagues [29] prospectively evaluated 61 patients treated with SBRT for colorectal metastases to 45 Gy in three fractions and observed severe liver

toxicity in one patient who died of hepatic failure 7 weeks after completing radiation; 60 % of the liver received ≥10 Gy.

– Princess Margaret Hospital performed two phase I trials of SBRT for primary liver tumors [30] and liver metastases [31] deriving total SBRT dose from a normal tissue complication probability (NTCP) modeling.
  - The study included patients with primary hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and hepatic metastases.
  - Approximately 17 % of patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma were found to progress from Child-Pugh A to B within 3 months after radiation.
  - In contrast, there were only two grade 3 liver enzyme changes in the liver metastases cohort, likely demonstrating that those with liver metastases present with healthier baseline liver parenchyma.

- To minimize the risk of RILD, the current QUANTEC recommendations suggest that mean normal liver dose should be less than 6 Gy for primary liver cancer and Child-Pugh B undergoing 3–6 Gy per fraction [24].
- However, in contrast to patients presenting with hepatocellular carcinoma, the majority of patients with hepatic metastases do not present with underlying cirrhosis and are therefore less susceptible to RILD.

18.8.2 Chest Wall Toxicity

- Chest wall pain and rib fracture, while rare, can be very painful. The most commonly used metric is the volume of chest wall receiving ≥30 Gy (V_{30}) [32–34].
- Dunlap and colleagues [34] combined SBRT data in lung cancer from multiple institutions, including 60 patients treated with three to five fractions of SBRT to peripheral lung lesions.
  – Reported no incidences of pain or fracture when the V_{30} was maintained below 30 cc, whereas 30 % of patients experienced chest wall toxicity when the V_{30} exceeded 35 cc.
- Cleveland Clinic group validated the findings of V_{30} and went further by developing a modified equivalent uniform dose (mEUD) model, accounting for variability in dose-fraction regimens and inhomogeneity [35].
- Memorial Sloan-Kettering Cancer Center prospectively followed 126 patients treated with SBRT with doses ranging between 40 and 60 Gy in 3–5 fractions for non-small cell lung cancer and found chest wall V_{30} ≥70 cc significantly correlated with grade 2 or higher chest wall pain [36].

18.8.3 Gastrointestinal Toxicity

- Peripheral and hilar liver lesions may place patients at risk for gastrointestinal toxicities including ulcerations and perforations.
- Blomgren and colleagues [7]: one patient experienced hemorrhagic gastritis when less than one-third of the stomach received more than 7 Gy, another patient had a duodenal ulcer after the distal stomach, and proximal duodenum received 5 Gy in four treatments.
- Hoyer and colleagues [29]: one patient experienced a colonic perforation, which required surgical intervention, and two additional patients had duodenal ulcers, which were treated conservatively.
- Additional SBRT studies suggest that the point dose to the duodenum should not exceed 10 Gy per fraction for three fraction regimens [15]. In all three settings, intestinal doses exceeded 30 Gy [15, 37].
- More recent trials using conservative dose constraints have reported minimal gastrointestinal toxicity, and normal tissue tolerance estimates for single and multiple fraction SBRT have been published [38].

Organ at risk	Dose constraints (QUANTEC)	Dose constraints RTOG 0438 (hypofractionation)
Liver	≥700 cc of normal liver receives ≤15 Gy in 3–5 fractions Mean normal liver dose: <15 Gy in 3 fractions or <20 Gy in 6 fractions	V_{27} less than or equal to 30 % V_{24} less than or equal to 50 %
Spinal cord	Max dose <50 Gy (0.2 % risk myelopathy)	Max dose ≤ 34
Stomach	D_{100} <45 Gy (<7 % risk ulceration)	Max dose 37 Gy to 1 cc
Small bowel	V_{45} <195 cc (<10 % risk grade 3 + toxicity) (peritoneal cavity)	Max dose 37 Gy to 1 cc
Bilateral kidneys	Mean <15–18 Gy (<5 % risk clinical dysfunction)	No more than 33 % of combined volume ≥18 Gy

18.9 Future Directions

- Delivering SBRT to large tumors (>7 cm) continues to be a challenge and in general was an exclusion criteria in the currently published prospective studies discussed.
  - Novel planning and delivery techniques are necessary to approach these larger tumors with similar ablative doses, while minimizing toxicity.
  - Further, tumors adjacent to critical structures including bowel also pose a challenge.
  - A recent strategy to treat these larger tumors discussed by Crane and Koay [39] is called simultaneous integrated boost (SIB) with simultaneous integrated protection (SIP).
    - The technique involves hypofractionation to achieve a biologically equivalent dose (BED) of 100 Gy in 15–25 fractions, followed by decreasing the CTV and PTV margins within normal liver tolerance, creating margins around organs at risk (OARs), and then treating the hypoxic center of the tumor to a BED >140 Gy if possible.
- Improvements in imaging to delineate normal liver parenchyma will also be important, and there are currently several imaging modalities being investigated [39].
  - Indocyanine green (ICG) is a water-soluble compound that binds to albumin and is selectively taken up by hepatocytes.
    - Its uptake correlates with hepatic function and can be used during planning to attempt sparing of normal liver tissue.
  - Sulfur colloid technetium 99 single-positron emission CT/CT is another imaging modality that can localize functional from nonfunctional liver tissue.
  - Eovist (gadolinium-ethoxybenzyl-diethylenetriamine) is another molecule which can be taken up by hepatocytes and correlates with normal liver tissue [39].
- Additionally, better management of respiratory motion is needed to achieve higher ablative doses.
  - Newer technologies are constantly being introduced.
  - Poulsen and colleagues [40] recently published feasibility results in their study using respiratory gating based on internal electromagnetic monitoring during liver SBRT.
    - Two patients with solitary liver metastases undergoing SBRT were implanted with electromagnetic transponders, using the Calypso® system (Varian Medical Systems, Palo Alto, CA).
    - Electromagnetic transponders are implanted percutaneously in or around the lesion. A 4DCT scan and breath hold end-exhale CT scan are obtained for planning.
    - During treatment, the treatment beam is gated based on positioning of the three transponders; when the transponders deviate more than 3 mm in the left-right

or anterior-posterior direction or more than 4 mm in the cranio-caudal direction, the treatment beam turns off.
    - With gating, they found the mean geometric error in any direction to be 1.2 mm.
- Lastly, to reach higher ablative doses, newer approaches are needed to reduce toxicity to surrounding organs at risk.
  - Biologic mesh spacers (BMS)
    - Yoon and colleagues [41]: the use of BMS to displace nearby organs from the liver, including the stomach, duodenum, small bowel, and colon.
    - BMS typically is placed laparoscopically and secured to adjacent soft tissue or liver using 10 mm clips or intracorporeal sutures.
    - In their study, Yoon and colleagues [41] performed this technique in 14 patients who were then treated with radiation (median dose 54 Gy in 5–15 fractions).
    - At 1 year, only one patient experienced grade 3 abdominal pain, and there were no additional grade 3–4 gastrointestinal toxicities.
    - Of the 12 patients treated, 11 had local disease control.
- Future techniques to enable higher doses to tumors in sensitive areas including the liver are highly needed.

Conflicts of Interest The authors have no conflicts of interest to report.

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