Colorectal Cancer Liver Metastases

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12.1 Introduction

Management of patients with metastatic colorectal cancer, in particular those with liver metastases, involves the convergence of multiple medical specialties and treatment approaches. Both systemic and local-regional (liver-directed) therapies should be considered for each patient. In a broader context, treatment of patients with

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colorectal liver metastases has been an exemplary platform for multi-disciplinary care, discussions about the putative oligometastatic disease state, and the use of local-regional treatments for the potentially curative treatment of patients with metastatic disease.

12.2 Surgery

The liver is a common site for the development of metastatic lesions in patients with hematogenously spreading colon and rectal cancer. Approximately, 30–50% of patients with colon and rectal cancer will develop liver metastases, either in the synchronous or metachronous setting [1, 2]. Classical autopsy data indicate that the liver may be the only site harboring evident metastatic disease in a reasonable proportion of patients [1]. Thus, eradication of these metastases can be considered potentially curative [2, 3].

Surgery has been the primary local therapy for colorectal cancer liver metastases (CRLM) for decades. Despite lack of high-level evidence in the form of randomized trials, resection of CRLM in selected patients is a largely accepted clinical practice. Part of this acceptance comes from publication of long-term follow-up from institutional series, which indicate the potential for long-term survival in selected patients. Fong and colleagues reported on survival outcomes for 1001 patients with CRLM who underwent resection [4]. For all patients, actuarial survival at 5 years was 37%. A number of variables were independently associated with survival, including the number of liver metastases, the presence of extrahepatic disease, and disease-free interval (from the time of the primary tumor to the development of metastatic disease). In a review of 1600 patients treated at Memorial Sloan-Kettering Cancer Center, 5-year *recurrence-free* survival ranged from 27 to 33% depending on the era of treatment [5]. Across large resection series, 5-year survival has been on the order of 35–58% [reviewed in [2]].

Surgery can take the form of anatomic resections, with removal of defined segments of the liver, or non-anatomic procedures such as wedge resections. Surgery affords the opportunity to both directly examine the liver and use intraoperative ultrasound for the detection of small lesions which may have been unappreciated on preoperative cross-sectional imaging [6].

Proponents of surgery argue that the reported clinical results are superior to what would be obtained with no treatment or systemic therapy alone. However, it is the issue of selection bias that is the foundation for much of the residual controversy over the use of surgery (and, by extension, any local therapy) for patients with CRLM [7].

Patient selection factors for surgery have changed over time, with the focus shifting away from the extent of tumor removed and toward the extent of normal liver left behind following the surgery [8]. This is the subtle but important principle of the organ's "critical volume," which is also a useful consideration in other, non-surgical, local treatments for liver tumors, including radiation therapy [9, 10]. In the context of surgery and ablative therapies, the critical volume is the minimum volume of

liver parenchyma and biliary and vascular supply that can meet the patient's physiologic and metabolic demands. A future liver remnant (FLR) volume of 20% is considered sufficient in otherwise healthy livers, and higher percentage volumes are required in the setting of prior extended exposure to chemotherapy or with underlying liver disease such as cirrhosis [reviewed in [2]]. Redundancy of function in the organ is the basis of this principle. In the terminology of classical radiobiology, the liver harbors a substantial reservoir of subunits, in anatomical-functional parallel arrangement [9]. Elimination of these subunits by surgery or ablative treatments does not necessarily render the organ as a whole non-functional, so long as a critical amount of subunits remain in the postsurgical FLR. In patients for whom the predicted FLR following surgery is insufficient, portal vein embolization (PVE) can be considered. With this procedure, the left or right branch of the portal vein is embolized, leading to atrophy of the treated hemi-liver and hypertrophy of the contralateral hemi-liver [reviewed in [2]]. This hypertrophy may increase the FLR volume (in the range of 10%) to an adequate level to allow for extended liver resections for patients with large and/or multi-focal tumors [[11], and reviewed in [2]]. PVE can also be combined with a two-stage resection approach [12]. This is performed when there is concern about rapid growth of disease within the FLR. Metastases in the FLR are resected or ablated first, followed by PVE to the contralateral hemi-liver, followed by the planned extended resection.

The main limitations of surgery include the need for the patient to be medically operable, i.e., able to tolerate a major operation, taking into account comorbidities including baseline underlying liver disease; the need to leave a critical volume of liver/sufficient FLR, again taking into account the functionality of the remnant organ; as well as anatomical considerations, such as location of the tumor with respect to critical structures such as inferior vena cava, which may increase the risk of a margin-positive resection [13].

Some patients will present with synchronous tumors—an intact primary colon or rectal cancer and liver metastasis/es. This situation raises a host of questions relating to sequencing of surgery for the primary tumor and the liver metastases, the role and timing of systemic therapies, and in the case of rectal cancer, the role and timing of radiation therapy. There is no clear consensus as to the appropriate sequencing of therapies [14]. However, there is general agreement that all sites of gross disease must ultimately be addressed with local therapies if the intent of the treatment course is for cure.

12.3 Embolization and Thermal Ablation

A wide variety of non-surgical liver-directed treatments exist for the treatment of CRLM and other liver tumors. These include arterial embolization therapies, thermal ablation treatments, and radiation therapy. The use of embolization is predicated on the dual blood supply to the liver—the normal liver parenchyma is primarily perfused by the portal vein and its branches, whereas tumors in the liver are exclusively or almost exclusively supplied by branches of the hepatic artery [15].

Embolization with particles occludes blood supply to liver tumors and can be combined with chemotherapeutic agents (chemoembolization), including drug-eluting beads, or radiation, such as yttrium-90 radionuclides associated with glass spheres or resins [16, 17]. Thermal ablation treatments typically take the form of percutaneous probe-based treatments, including radiofrequency and microwave ablation (RFA/MWA) (extreme heat) and cryoablation (extreme cold) [Reviewed in [18]]. These treatments can also be used during open or laparoscopic liver resections as well, potentially as part of a combination approach with resection. Radiofrequency ablation results for patients with colorectal liver metastases are available and show results which rival those of surgical series in highly selected cohorts of patients. Oshowo and colleagues compared the results of surgery and RFA for the management of solitary CRLM [19]. Survival at 3 years was over 50% and nearly identical in the two groups. RFA or MWA are not widely accepted, however, as alternatives to resection in CRLM patients who are medically operable. This is due to a number of reasons, including fundamental limitations of thermal ablation (discussed below) and lack of randomized comparison [20].

The main limiting factors for the success of thermal ablation include tumor size; technical approach, with the percutaneous approach potentially leading to inferior outcomes relative to intraoperative use; and abutment of high-caliber vessels which may lead to inadequate heating by a cooling/heat-sink effect (more problematic for RFA relative to MWA) [21–23].

12.4 Radiation Therapy

The routine consideration of radiation therapy for the management of CRLM and other liver tumors is a relatively recent development in clinical oncology. Historically, there has been concern for the induction of (classical) radiation-induced liver disease (RILD), a potentially fatal syndrome classically seen in patients who have undergone irradiation of the whole liver or a large volume of it [24, 25]. The dose associated with development of RILD (around 30 Gy delivered with a conventionally fractionated treatment course) is well below that needed for eradication of CRLM. In modern times, risk of RILD is of particular concern for patients receiving radiation therapy for colorectal liver metastases as most of these patients have been heavily treated with multiple chemotherapy regimens, which has been associated with chemotherapy-associated steatohepatitis (CASH). However, a number of developments have changed the perception of liver irradiation in recent years. These include (1) an appreciation of volume effects in the liver, predicated on its generally parallel anatomical-functional arrangement and exemplified in the promising results of three-dimensional conformal partial liver irradiation, and (2) continued improvements in technology and treatment planning, which have allowed for substantial dose escalation to liver tumors while limiting irradiation of non-targeted liver tissue. Details of these technological improvements and practical means of implementing them in the treatment of CRLMs are discussed later in this chapter.

Pioneering work from investigators at the University of Michigan demonstrated the ability to escalate dose to focal intrahepatic tumors, while keeping the risk of classical

RILD and non-classical RILD low [26]. These studies made use of three dimensional conformal radiation treatment planning. Subsequently, in the 1990s and 2000s the field of extracranial radiosurgery evolved [27]. This approach took inspiration from stereotactic intracranial radiosurgery. Safely delivering radiosurgery requires extreme treatment precision and accuracy and a steep gradient of dose outside of the targeted lesion. The latter is achieved through the use of radiation delivered by a multitude of beam directions, including non-axial and non-coplanar arrangements.

Herfarth and colleagues reported on a phase I study of single-fraction liver irradiation, making use of a stereotactic body frame, for patients with liver tumors [28]. Other phase I studies of single-fraction treatments have also been reported [29, 30]. Rusthoven and colleagues conducted a phase II study of 3-fraction liver SBRT, with excellent local control results through 18 months median follow-up [31]. Other phase II and institutional studies, including studies specifically evaluating the treatment of CRLMs, also have demonstrated promising local control results in selected patients [32–34]. Recently, using a prescription dose of 25 Gy × 3 fractions, Scorsetti et al. demonstrated a 91% local control rate at 2 years for colorectal liver metastases [34].

Given the challenges associated with delivering tumoricidal radiation doses in the setting of the radiosensitive liver, there is interest in alternatives to external photon beam irradiation. These include the use of particle therapies such as proton and carbon ion beams; interstitial brachytherapy; and radioembolization. Ion beam therapy carries the physical advantage of the Bragg peak, with overall reduced energy deposition in organs at risk relative to photon irradiation. Carbon ion beams also have potential biological advantages relative to protons and photons [35]. Facility costs have limited the number of particle facilities available, but the number of centers is increasing. High dose-rate (HDR) interstitial brachytherapy is not widely used, but has an advantage relating to its steep dose gradients [36].

Radioembolization, also known as selective internal radiation therapy, involves the intra-arterial delivery of radionuclides (yttrium-90) bound to glass or resin spheres. The main promise of radioembolization is concentrated delivery of yttrium-90, which undergoes β decay with limited path length, to tumors by virtue of the blood supply [37]. Large volume or more focal radioembolization (radiation segmentectomy) treatments can be delivered [38]. The SIRFLOX trial randomized patients with liver-only or predominant metastatic colorectal cancer to treatment with systemic therapy or systemic therapy and radioembolization [39]. The primary endpoint of the trial was progression-free survival (at any site, including the liver). The difference between the two groups was not statistically significant. However, time to progression in the liver was substantially prolonged in the patients treated with radioembolization.

12.5 Systemic Therapy

Systemic therapies for the treatment of metastatic colorectal cancer have undergone substantial evolution in recent years. Treatment with 5-Fluorouracil remains a key component of systemic regimens, but a number of additional agents have been introduced and found effective in combination regimens, including classical cytotoxic drugs such as oxaliplatin and irinotecan [reviewed in [40]]. Drug agents which

target vascular endothelial growth factor (VEGF) and other components of angiogenesis as well as the epidermal growth factor receptor (EGFR) have also found utility in the treatment of metastatic colorectal cancer [reviewed in [41]]. More recently, immunomodulating drugs have been under study, with evidence of efficacy in selected patients [42].

Chemotherapy can be delivered by the conventional intravenous route or by hepatic arterial infusion (HAI) [reviewed in [43]]. The latter approach seeks to take advantage of the arterial-based perfusion of liver metastases as well as pharmacologic benefits of high liver extraction of certain chemotherapy drugs. Although generally associated with high response rates, HAI carries the risk of biliary toxicity, and its value in the setting of modern systemic regimens is uncertain. Increased response rates may convert patients with initially unresectable disease to resectable status, but this is also a controversial issue.

Although widely used in the treatment of patients with metastatic colorectal cancer, the value of systemic therapy in patients with *resectable* metastatic disease is controversial [44]. Systemic therapy may have special value in the setting of CRLM where the lesions are considered borderline resectable because of volume of disease or association with critical vascular structures, in which case cytoreduction may render the metastases resectable [45, 46]. The value of systemic therapy in patients for whom radiation is planned as the primary curative-intent liver-directed treatment is also uncertain. Cytoreduction with systemic therapy may be of additive value in this situation. In the setting of very bulky liver metastases, for whom radiation therapy is planned, treatment with up-front systemic therapy may lead to substantial cytoreduction and a reduction in the target volume for the radiation course. However, systemic therapies used to treat metastatic metastatic colorectal cancer can injure the liver through a variety of mechanisms, making subsequent surgical or ablative treatments (including SBRT) more risky. Sinusoidal obstruction, the histopathological basis of liver veno-occlusive disease, is one of the risks associated with chemotherapy, in particular oxaliplatin [47]. Of note, a similar histopathological picture is the underlying basis of classical RILD [24]. Careful assessment of liver function, through laboratory studies and possibly specialized imaging, prior to planned liver-directed therapy is critical [48]. The radiation oncologist must also be aware that therapies which target angiogenesis have also been associated with significant normal tissue toxicity, in particular bowel toxicity, when delivered around the time of abdominal irradiation [reviewed in [49]]. Strict guidelines as to the sequencing of these treatments are not yet available, but potentially serious interactions between these treatments must be considered, especially when bowel is close to the liver target volume.

12.6 A Multi-Disciplinary Approach: Patient Selection

The patient with CRLM can thus be seen to have both systemic and liver-directed therapies as treatment options, the latter to include a multitude of different approaches ranging from open surgery to more minimally invasive therapies. The

judicious use of local therapies in the patient with metastatic disease is perhaps one of the most important and challenging decisions to be made during the treatment course for patients with metastatic colon or rectal cancer. This question may in fact arise several times during a given patient's course, usually in the context of ongoing effective systemic therapy.

A number of variables need to be addressed when considering liver-directed therapies for patients with CRLMs. Chief among these, and perhaps the most difficult consideration, is an assessment of the biological behavior of the tumor. Surrogates for aggressive behavior, including the presence of "widespread" extrahepatic metastases, should be considered. It is generally accepted that local therapies for liver metastases in this setting are unlikely to meaningfully impact survival metrics. Moreover, in this situation, complications from local therapies may delay the use of systemic therapies, and thus, lead to worse survival outcomes. In the future, molecular studies, such as miRNA analysis, may indicate which patients with metastatic disease truly fit into the category of "oligometastatic" cancer, and thus, would be most likely to benefit from the use of local treatments [50]. Also of note, some patients with "polymetastatic" cancer may indeed be treated with local therapies if there is the goal of synergizing with systemic therapies, such as immunomodulating systemic treatments [51]. This is an active area of clinical research interest [52].

For the reasons discussed above, surgery is usually considered the "gold standard" approach to patients who indeed have resectable liver metastases and who are otherwise considered good candidates for liver-directed treatments. Non-surgical therapies such as thermal ablation and radiation therapy may be considered in patients who are not surgical candidates because of medical comorbidities, anatomical constraints, or patient choice. To the best of the author's knowledge, there are no randomized data comparing thermal ablation with radiation therapy for the treatment of liver metastases. The RAS01 study was a randomized comparison of RFA and stereotactic body radiation therapy (SBRT) for the treatment of patients with CRLMs. However, this study closed because of inadequate accrual (information available at: https://clinicaltrials.gov/ct2/show/NCT01233544?term=RAS01&rank=1).

Tumor size and location may be of help in deciding between percutaneous thermal ablation and high-dose hypofractionated radiation therapy. Large tumor size and abutment of large-caliber blood vessels limit the efficacy of RFA. Lesions near the hilum of the liver or near the dome may be difficult to access with a percutaneous approach and/or place the patient at significant risk for biliary, bowel, or pulmonary complications from the procedure; treatment of hilar lesions may also be challenging for radiation due to the proximity of large bile ducts and bowel, which may limit the amount of radiation that can be delivered depending on the exact location. In special circumstances, "spacer" material may be placed before ablations or radiation therapy to put space between critical organs and intrahepatic targets [53, 54].

Data from the University of Michigan, in patients with hepatocellular carcinoma (HCC), showed improved freedom from local progression with the use of SBRT as opposed to RFA for larger (>2 cm) tumors [55]. The strict applicability of these data to patients with CRLM or other types of metastases, however, is of course uncertain. Stintzing and colleagues compared CyberKnife radiosurgery (27 Gy in one

fraction) with RFA for patients with CRLMs [56]. Patients were matched for clinical features. One-year local control rates were similar between the two groups (85% for radiation and 65% for RFA).

Microwave ablation and new techniques such as irreversible electroporation, which may provide greater efficacy and safety compared to RFA depending on the context, will also need to be considered in comparison with SBRT [reviewed in [57]].

Table 12.1 outlines potential treatment options for colorectal liver metastases during different clinical scenarios.

Table 12.1 Potential treatment options for colorectal liver metastases

Local treatment modality	Appropriate clinical scenario
Surgery[a]	Complete resection must be feasible based on anatomy and extent of disease, with appropriate future liver remnant taking into account the patient's baseline liver function[b] Patients presenting with synchronous disease—resectable metastatic disease and an intact primary tumor—should be planned for resection of all sites of gross disease if the treatment intent is curative When insufficient liver volume is initially present, preoperative portal vein embolization with or without staged liver resection can be considered to increase the future liver remnant size Re-resection can be considered in selected patients in the setting of otherwise controlled systemic disease and adequate hepatic function
Ablation[a]	Ablative therapies, including RFA, microwave ablation, and cryoablation, are reasonable treatment options for non-surgical patients. These techniques may be limited by anatomical considerations such as proximity to vasculature and baseline hepatic function
Hepatic arterial infusion (HAI)	Placement of a hepatic arterial port or implantable pump during surgery with chemotherapy infusion directed to arterially perfused liver metastases may be considered as a regional treatment option in the setting of unresectable liver metastases; this approach may also convert unresectable disease to resectable status. Biliary toxicity is a concern. HAI should only be considered selectively at institutions with extensive medical and surgical oncology experience with this procedure
Arterial-directed embolic therapy (TACE)	Trans-arterial embolization of liver metastases, with local delivery of chemotherapy as part of the procedure, often with the use of drug-eluting beads, alone or in combination with systemic therapy, may be an option in selected patients
Radioembolization	Arterially directed catheter therapy using yttrium 90 microspheres, selective internal radiation is an option in selected patients with predominant liver metastases. Unlike other ablative techniques, there is less limitation due to anatomical considerations and extent of disease, but hepatic function should be considered
3D CRT/IMRT/ SBRT radiotherapy	Highly conformal external beam radiation therapy may be considered in selected cases. As with ablation therapies, radiotherapy is not used in place of surgery in medically and antomically operable patients

[a]Ablative techniques may be considered alone in conjunction with resection as long as all original sites of disease are amenable to resection or ablation

[b]When considering local therapies for colorectal liver metastases, primary tumor should ideally have undergone R0 resection (plan for debulking < R0 resection not recommended) and there should be no evidence of uncontrolled extrahepatic disease

12.7 Radiation Therapy: Clinical and Planning Considerations

Once the key issue of patient selection has been addressed in multi-disciplinary discussion and a plan to move forward with radiation therapy is made, the radiation oncologist must consider multiple treatment planning problems. In this section, we consider these issues individually and present solutions when indicated. (Note that the issue of fiducial placement, which must precede simulation, is discussed in Sect. 12.7.7).

The reader is also referred to the AAPM Task Group 101 report on recommendations for SBRT planning [58].

12.7.1 Motion Management

Situated under the diaphragm, the liver is often highly mobile throughout the respiratory cycle. The internal target volume (ITV) is the envelope of space which encompasses the motion of the gross tumor volume (GTV). Treating GTVs which are very mobile, and thus have large ITVs, results in exposure of a higher volume of normal tissue to radiation.

A number of strategies are in common clinical use to mitigate this problem. These include: (1) Respiratory gating, in which the target is irradiated only during a certain portion of the respiratory cycle, often around end-expiration because of the relative stability of the target volume during this time period, with, in essence, a truncated ITV (relative to the non-gated, free-breathing situation); (2) Treatment in breath-hold, which can be considered an extreme form of gating, as the target is (nearly) motionless near end-inspiration or end-expiration; (3) Abdominal compression, which uses a physical device to limit diaphragmatic motion and thus limit liver excursion; and (4) Tracking, such as used with the CyberKnife Synchrony (Accuray, Sunnvale, CA) system, which uses external surrogates to follow internal tumor motion [59–62]. All of these approaches have value and their specific use depends on physician and institutional preference as well as patient tolerance.

At the author's institution, abdominal compression and breath-hold techniques are used for patients with mobile liver metastases.

Abdominal compression as practiced at our institution involves the use of a plastic plate placed inferior to the xyphoid and ribs [63]. A compression screw is used to apply pressure to the plate. Fluroscopy is used to determine the decrement in upper abdomen/diaphragm motion, and pressure gradually and iteratively applied to limit motion to <1 cm, and preferably <5 mm. Coaching of the patient throughout the process is critical to ensure a stable breathing pattern.

For the breath-hold simulations and treatments at our institution, the Active Breathing Coordinator (ABC) (Elekta, Stockholm) is used. With this device, the patient's respiratory cycle is monitored. At a selected threshold, inflow of air is sealed and the breath-hold begins. The device works as a spirometer, with the

threshold set as a volume of gas that is inhaled beyond the patient's functional residual capacity. Patient should be coached to adopt a steady breathing rhythm [64]. The treating physician should be aware of intra-fractional differences in tumor position that may occur during the treatment process with each repeated breath-hold [65, 66]. These differences can be assessed at the time of simulation by performing multiple CT scans in breath-hold or by imaging with fluoroscopy and measuring differences in position of a surrogate structure (such as the diaphragm) relative to some fixed anatomy (such as the spine). These intra-fractional positional differences need to be considered in the design of the planning target volume (PTV).

12.7.2 Simulation: Immobilization

Strict but tolerable immobilization is essential to limit unexpected patient and tumor motion during the radiation treatment delivery. A variety of means of achieving this goal are widely used in radiation oncology clinics. At the author's institution, we use a stereotactic body frame (Elekta, Stockholm) with a custom-fit vacuum pillow placed inside the body frame. This approach has proved very useful, with results from a report by Foster et al. showing minimal intra-fractional motion for multiple treatment sites [63, 67].

12.7.3 Simulation: Use of Contrast for Target Delineation

Identification of the tumor targets within the liver is one of the most critical, and challenging, parts of the treatment preparation process. As previously discussed, the liver receives dual blood supply, from the hepatic artery and the portal vein, with arterial supply the main source of perfusion to liver tumors [15]. Moreover, colorectal liver metastases tend to be poorly vascularized tumors [68]. Thus, they are often best appreciated during the portal venous phase of a CT scan with contrast. In this phase, the metastatic lesion will appear hypodense relative to the enhancing normal liver tissue. It is often helpful to evaluate available diagnostic CT studies prior to CT simulation to determine which phase(s) will be most helpful to obtain during the simulation.

Once the phases of interest are identified, the timing of imaging relative to the start of the contrast injection needs to be established. Bolus tracking is one feature which may allow for good timing of the arterial phase. If bolus tracking is not available, the scans need to be timed properly to achieve the desired phase. Also of importance are the type of contrast (specifically, the concentration of iodine) and the rate of contrast injection.

At the author's institution, the following scan parameters are used. Isovue (iopamidol) 300 or Isovue 370 iodinated contrast is used and injected at a rate of 3–4 mL/s. For this dose rate, a 20 gauge IV catheter is used. For smaller-bore catheters, an infusion rate of 2 mL/s is used. For late arterial-phase imaging, the scan is timed so that the liver is imaged about 40 s after the contrast infusion is started. For portal venous-phase imaging, the timing is 65 s, and for delayed-phase imaging, the timing is about 3 min. The author also typically obtains a non-contrasted study at the beginning.

12.7.4 Target and Normal Tissue Delineation

For CRLM treatment planning, usually the non-contrast and portal venous-phase scans are fused on the basis of spine matching. In the author's practice, the non-contrast scan is used for treatment planning. When the ABC system is used, the GTV is identified. Typically, no margin is added to the GTV to create a clinical target volume (CTV); hence, the CTV equals the GTV. In the setting of treatment of recurrent disease following prior liver resection, in which the recurrence is close to the original resection site, margin can be considered over concern for meaningful extension of microscopic tumor beyond the edges of what is radiographically visible.

When the abdominal compression system is used, an ITV is generated based on delineation of the GTV on the various respiratory phases (at the least, the 0 and 50 phases). For hypodense targets, the reconstructed minimum intensity projection (MinIP) set may be of use in identifying the ITV.

Expansions from the CTV/GTV and the ITV (in the case of abdominal compression) to the PTV depend on a number of factors. These include the robustness of immobilization, the use of image-guidance to make adjustments prior to treatment, and concerns about any residual motion not addressed by the ITV. Typically, in the author's practice an expansion of 0.5–1 cm is made, isotropically.

A variety of normal structures are at risk when using radiation to treat targets in the upper abdomen. Many of these structures are hollow organs which behave as serial structures, such as the intestines, stomach, and spinal cord/cauda equina, in which high doses to even low volumes may cause serious consequences. In many situations, it will be the (uninvolved) liver itself which may be dose-limiting. Various liver toxicities can be seen clinically, including RILD, characterized by ascites and anicteric liver enlargement, with a substantial increase in alkaline phosphatase levels [25]. "Nonclassic" RILD has been defined as significant increases in hepatic enzymes without features of classic RILD [25].

Also as discussed above, the liver parenchyma has parallel functional-anatomical arrangement. For such organs, high doses to limited volumes are not expected to

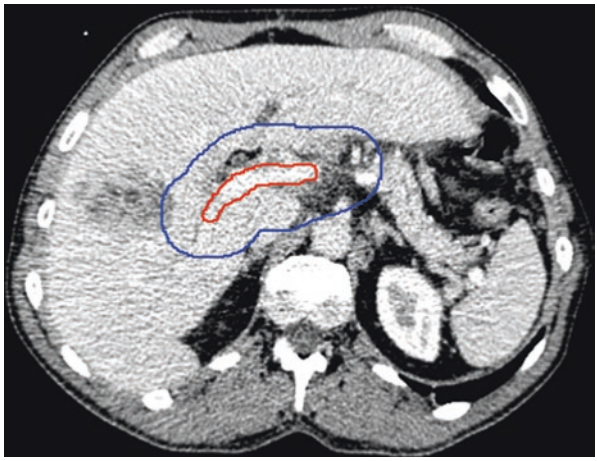

Fig. 12.1 The central liver zone (*blue contour*) has been defined as a 2 cm isotropic expansion surrounding the path of the portal vein (*red contour*) to its bifurcation point(s) within the liver. Note the hypodense liver metastasis immediately lateral to the central liver zone in this portal venous phase scan

generate clinically relevant toxicity. It should be noted, however, that near the hilum of the liver, with the coalescing biliary system as well as the portal vein and hepatic artery, the liver should be considered to have more of a serial structure. Damage to these structures can have substantial consequences to the remaining liver parenchyma. Such a transition is similar to the central lung structures. Distinct biliary toxicity has been reported in cases of central liver SBRT [69]. At our institution, we used a "central liver zone" in a phase I dose-escalation study to exclude patients from getting very high single-fraction doses of radiation [30]. This zone was defined as the course of the portal vein to its bifurcation within the liver, expanded by 2 cm, analogous to the central lung zone considered in lung SBRT [70]. Of note, Eriguchi and colleagues used a similar approach to define the central liver and found that a prescription dose of 40 Gy in five fractions was tolerable with respect to biliary complications [71]. An example of central liver zone target volume is represented in Fig. 12.1.

Suggested liver constraints are shown in Table 12.2. The radiation oncologist should assess baseline liver function by evaluation of the liver's synthetic function (albumin and coagulation study results) as well as the bilirubin and hepatic enzyme levels. The liver constraints shown in the table refer to patients without significant underlying liver disease. More conservative measures must be considered in the setting of cirrhosis or other liver disease [72]. It should be emphasized that this Table is simply a guide with general recommendations and that many of the constraints are not rooted in a large body of supportive clinical data. Please refer to the table and its legend for more details. Future clinical results should help refine these constraints.

Table 12.2 Normal tissue constraints for liver SBRT[a]

	1 Fraction	3 Fractions	5 Fractions	Other references
Liver[b]	700 cc gets <9.1 Gy	700 cc gets <15.1 Gy	700 cc gets <21.5 Gy	
Stomach[a]	Maximum point: 12 Gy	Maximum point: 24 Gy	Maximum point: 30 Gy	
Small intestine and colon[a]	Maximum point: 12 Gy	Maximum point: 24 Gy	Maximum point: 30 Gy	[73, 74]
Spinal cord	Maximum point: 14 Gy <0.35 cc gets >10 Gy	Maximum point: 22.5 Gy <0.35 cc gets >15.9 Gy	Maximum point: 28 Gy <0.35 cc gets >22 Gy	
Skin	Maximum point: 27.5 Gy <10 cc gets >25.5 Gy	Maximum point: 33 Gy <10 cc gets >31 Gy	Maximum point: 38.5 Gy <10 cc gets >36.5 Gy	
Esophagus	Maximum point: 16 Gy <5 cc gets >11.9 Gy	Maximum point: 27 Gy <5 cc gets >17.7 Gy	Maximum point: 52.5Gy <5 cc gets >27.5 Gy	Adapted from RTOG 06-31
Heart	Maximum point: 22 Gy <15 cc gets >16 Gy	Maximum point: 30 Gy	Maximum point: 52.5Gy <15 cc gets >32 Gy	Adapted from RTOG 06-31

[a]These are institutional (University of Texas Southwestern Medical Center) constraints, authored by Robert Timmerman, MD. The stomach and duodenum constraints are those used specifically by the author of this chapter (J. M.) "Point" volumes are defined as 0.035 cc or less. The "Other References" column gives references to various published literature which analyze clinical data regarding dose constraints. The issue of dose constraints for bile ducts is discussed in the text

[b]For the liver, the greater of 700 cc **or** 1/3 of the organ's volume (preceding resection or other means of liver volume reduction) is chosen as the constraint. As an example, if the patient's liver is 2400 cc, then the volume constraint is 800 cc (= 1/3 of 2400 cc), **not** 700 cc. Conversely, the reader will note that the 700 cc constraint may be considered overly restrictive for patients with smaller livers (livers less than 2000 cc in volume). The radiation oncologist must consider the reason for the small liver volume—for example, if it is in the setting of cirrhosis. In that setting, maintaining a requirement for more strict liver sparing, such as 700 cc, is appropriately more conservative than allowing for 1/3 of a volume much less than 2000 cc

12.7.5 Dose Selection

As previously discussed, a number of dose-fractionation prescriptions have been studied and reported. SBRT courses are delivered in 1–5 fractions. In the author's practice, dose selection is based on the ability to meet the OAR dose constraints, taking into account underlying liver function, as well as location of the tumor within the liver (see discussion above). Common dose prescriptions are shown in Table 12.3. Typical dose requirements are the following: dose is prescribed to PTV coverage, with the D95 for the PTV set at the prescription dose; the minimum dose in the PTV should be 90% of the prescription. This latter objective allows for some degree of "underdosing" of the PTV when it expands into critical structures.

Table 12.3 Liver SBRT dose prescriptions[a]

1, 3, and 5 fraction regimens	Tumors in the central liver zone[b]	Tumors outside of the central liver zone[b]
1 Fraction	–	30 Gy × 1 fraction [29] 35 Gy × 1 fraction [30] 40 Gy × 1 fraction [30]
3 Fractions	–	18 Gy × 3 fractions = 54 Gy
5 Fractions	10 Gy × 5 fractions	12 Gy × 5 fractions [75]

[a]Common prescriptions used in the author's practice, with supporting references as noted
[b]Central liver zone is defined as the course of the portal vein to its bifurcation within the liver expanded by 2 cm

Chang and colleagues evaluated local control results from three institutions and concluded that, for a 3-fraction SBRT course, a total dose of about 48 Gy would be needed for 90% likelihood of local control at 1 year for colorectal liver metastases [76]. Interestingly, in their analysis, although dose was associated with local control outcomes, tumor (GTV) volume was not.

It should be noted that the "stereotactic approach" to treatment planning can be applied to any dose-fractionation scheme, including more modestly hypofractionated treatment approaches. The therapeutic ratio for the treatment of very bulky tumors, or tumors abutting critical structures, may benefit from more and more protracted treatment course (while still hypofractionated relative to conventional radiation therapy) as opposed to lowering the dose-per-fraction for a 5-fraction course. Dose to the areas of abutment can be limited while still delivering a high dose to the bulk of the tumor. Tao and colleagues demonstrated the advantages to this approach in a large series of patients with cholangiocarcinoma [77]. The same principle can be applied to the treatment of select CRLMs.

12.7.6 Treatment Planning

As previously discussed, treatment planning principles for extracranial SBRT are inspired by intracranial radiosurgery practice. Traditional 2-, 3-, and 4-field treatment plans are not compatible with liver SBRT. A variety of treatment approaches can achieve the goal of high focal dose with sharp gradient. A single dynamic conformal arc can provide excellent coverage and OAR sparing, especially for spherical targets (Fig. 12.2). Another approach includes multiple conformal beams, including the use of non-axial and non-coplanar beams, similar to the "beam bouquets" previously described [78, 79]. For both of these 3D approaches to treatment planning, block

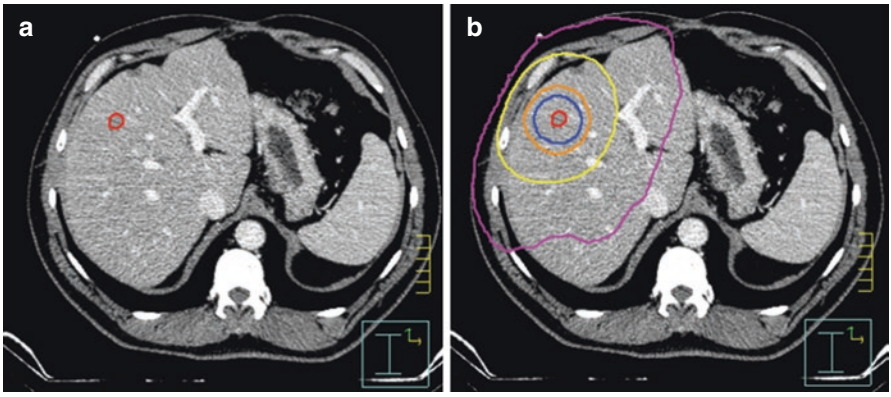

Fig. 12.2 A 50-year-old patient with known history of metastatic colon cancer presented with a growing lesion in segment V of the liver. The patient had undergone prior resection of multiple hepatic metastases. To treat the growing lesion in segment V, a course of SBRT was arranged. In (**a**), the hypodense lesion as detected on the portal venous phase of the CT simulation scans is outlined in *red* (GTV). Window/level are adjusted to maximize the conspicuity of the lesion. A portion of the stereotactic body frame is seen in this cropped image as well. In (**b**) the treatment plan with isodose line distribution is shown, planned on the preceding non-contrast scan and overlaid on this portal venous phase image. A dose of 30 Gy in one fraction was prescribed to the periphery of the PTV. A single dynamic conformal arc was used for dose delivery. *Red* interior circle is the GTV, *blue line* = 30 Gy, *orange line* = 20 Gy, *yellow line* = 10 Gy, *purple line* = 5 Gy. (Note: PTV not shown). (Treatment plan: Jonathan Dougherty, CMD)

margins around the target projection must be considered. Zero or even negative block margins, with prescription to a low isodose line, may provide the sharpest dose gradients surrounding the target, simultaneously leading to extreme hot spots within the target, replicating what is achieved with Gamma Knife radiosurgery [80]. This heterogeneity within the target may not be desirable if the target surrounds a critical structure.

Intensity modulation methods may also be of value, in particular for highly complex target shapes with concavities. Volumetric modulated arc treatments (VMAT) are another option (Fig. 12.3). When intensity modulation is used to treat a mobile target, consequences of the leaf interplay effect must be considered, especially for hypofractionated courses [81, 82]. IMRT/VMAT can be used to keep the dose within the target homogenous, if desired. Conversely, relaxing constraints on hot spots within the target can improve dose gradients outside of the tumor [83].

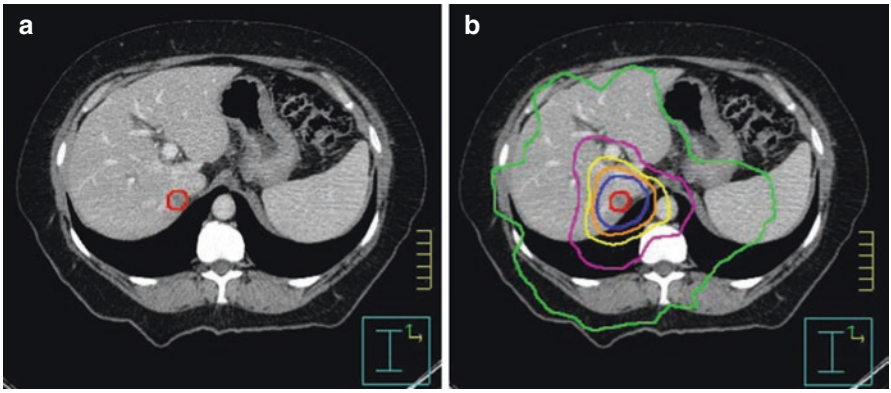

Fig. 12.3 A 52-year-old patient with known history of metastatic colon cancer presented with a lesion in segment VII of the liver, near the vena cava. The patient had undergone prior chemotherapy with reduction in size of the mass, but it persisted on imaging. In (**a**), the hypodense lesion as detected on the portal venous phase of the CT simulation scans is outlined in *red* (GTV). Window/level are adjusted to maximize the conspicuity of the lesion. A portion of the stereotactic body frame is seen in this cropped image as well. In (**b**) the treatment plan with isodose line distribution is shown, planned on the preceding non-contrast scan and overlaid on this portal venous phase image. A dose of 50 Gy in five fractions of 10 Gy per fraction was prescribed to the periphery of the PTV. This dose was based on the location of the tumor relative to the central liver zone. A volumetric modulated arc therapy plan was chosen based on the location of the tumor. *Red* interior circle is the GTV, *blue line* = 50 Gy, *orange line* = 40 Gy, *yellow line* = 30 Gy, *purple line* = 20 Gy, *green line* = 10 Gy. (Note: PTV not shown). (Treatment plan: Jonathan Dougherty, CMD)

12.7.7 Treatment Delivery

Image guidance is a critical component of SBRT delivery. At our institution, we use cone beam CT (CBCT) imaging for target localization prior to treatment. Final adjustments in patient positioning are made by couch adjustments. Other methods, such as tracking techniques used by the CyberKnife, are also available.

Intrahepatic tumors are typically not visible on CBCT imaging. Fiducial markers may play a role in helping to localize the area of interest prior to treatment. The decision to place fiducials must of course be made prior to the simulation. Without fiducial placement, the treating physician must rely on the liver, or region of target location within the liver, as a fiducial of sorts. Other anatomical structures may also provide guidance, as can clips or similar materials from prior surgeries. Although implanted fiducials have obvious advantages for localization, the risks of implanting them, including hemorrhage and fiducial migration, must be considered as well. There are little clinical data to support or refute the need for implant fiducials when treating liver tumors. Data from the University of Michigan show a potential benefit for their use in a series of patients treated for HCC, but the difference compared to patients treated without fiducials did not reach statistical significance [55].

12.8 Summary

Management of liver metastases presents a wide variety of challenges. Patient selection is the most critical and perhaps the most challenging step and demands multidisciplinary communication. For patients with CRLMs, the question of utilizing local therapies may be raised multiple times during a patient's clinical course. The application of local therapies to treat patients with metastatic disease, beyond palliation, is likely to increase as systemic therapies improve. Indeed, a number of clinical trials are evaluating this potential shift in tradition.

Radiation therapy has grown from a treatment with marginal applications for patients with liver metastases to become an important and viable alternative to surgery and non-surgical ablation options. Results with hypofractionated treatment courses have shown great promise with respect to tumor control and safety.

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