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Review

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Hypofractionated ablative radiation therapy for hepatocellular carcinoma: practical considerations and review of the literature

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. The prognosis for patients who present with inoperable primary liver tumors is poor with median survival times of 12 months or less. Tumor-related liver failure is a common cause of mortality, underscoring the importance of local control. Recent advancements in external beam radiation therapy delivery techniques have enabled dose escalation that in turn has significantly improved local control and has allowed radiation therapy to emerge as an effective modality in this setting. In this review, we outline the critical practical aspects of treating liver tumors with radiation including choice of fractionation, motion management, image guidance and use of intensity-modulated radiation therapy vs. proton beam therapy. We review our approach to ablative radiation therapy for HCC with consideration of underlying cirrhosis and provide a brief overview of the current literature.

Keywords: Hypofractionated ablative radiation therapy, stereotactic ablative radiotherapy, radiation, large hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is the second leading cause of cancer-related death worldwide. While surgical resection and/or transplantation represent well established curative options for early stage cancer in patients with compensated liver disease, other local treatments play an important role in more advanced patients, including patients with large locally unresect-

able tumors, liver dysfunction and extrahepatic disease. It is important to note that death in patients with unresectable HCC is often related to liver failure as a direct consequence of local tumor progression. The mechanisms of liver failure include functional liver parenchymal loss, biliary obstruction, portal venous obstruction, and hepatic venous outflow obstruction resulting in ischemia (Budd Chiari). Some of these may occur even with small tumors that are located near hilum or the confluence of the hepatic veins and inferior vena cava. Although not well studied in patients with HCC, data on direct causes of death from another primary liver tumor, intrahepatic cholangiocarcinoma, treated with radiation at The University of Texas MD Anderson Cancer Center demonstrated that death resulted from tumor-related liver failure in 89% of patients whose cause of death could be determined. Half of those deaths were from biliary obstruction and the other half from vascular compromise or a combination[1]. This underscores the importance of local therapies even for patients with advanced disease and suggests that effective local control may translate into a major survival benefit.

Current practice includes many options for liver directed-therapy in inoperable patients. Percutaneous image-guided ablative options (radiofrequency, microwave, cryoablation or percutaneous ethanol injection) are preferred for small peripheral tumors located away from segmental and main bile ducts, the liver surface, and major vessels. Additional options include arterially directed options such as bland transarterial embolization, transarterial chemoembolization or radioembolization with yttrium-90 beads. Radiation therapy is a complementary option for patients with liver tumors and is a preferred option for tumors near the biliary tree, hilum of the liver, main portal vein, or inferior vena cava. For large liver tumors, radiation therapy may be the most effective local therapy available.

Effective radiation therapy for liver tumors such as HCC is predicated on the ability to deliver ablative doses with minimal risk of injury to the surrounding normal structures including liver parenchyma, which is often compromised in this patient population-as well as the bile ducts, chest wall, stomach, duodenum and colon. A number of treatment related factors can improve the therapeutic ratio of liver radiation therapy (RT), including increasing the number of fractions, controlling respiratory motion, using soft tissue image guidance, and using proton therapy to spare liver. In the following sections we examine how these factors enable the delivery of ablative RT for HCC.

LIVER TOLERANCE

Historically, radiation therapy to the liver was thought to be unsafe based on the inability of the whole liver to tolerate doses exceeding 30 Gy[2]. Investigators from the University of Michigan subsequently showed that partial liver volumes can tolerate high focal doses of radiation, defined the radiation dose-response relationship for liver tumors, and described objective parameters to evaluate dose-volume relationships of ablative liver treatments[3,4].

Notably, radiation-related liver toxicities may have distinct mechanisms and presentations in patients with cirrhosis and without cirrhosis. Radiation induced liver disease (RILD) is now classified as either classic (triad of anicteric hepatomegaly, elevated alkaline phosphatase and ascites) or non-classic (jaundice and markedly elevated serum transaminases). Several reports have noted that patients with advanced cirrhosis are at a higher risk of non-classic radiation-induced liver disease[5-7]. Most recently, it has been recognized that patients who undergo radioembolization with ^{90}Y are susceptible to radioembolization-induced liver disease[8], which presents with jaundice and ascites in the absence of tumor progression. The mechanisms underlying these different presentations of radiation-related liver toxicities remain subjects of ongoing research; but it is clear that the dose-volume relationship is altered in the presence of limited liver reserve[5-7,9]. In addition to cirrhosis, other common reasons for limited liver reserve include limited normal-liver volume due to previous resection or hepatotoxic chemotherapy, and tumor-related dysfunction due to biliary or vascular

compromise. Indeed, owing to the presence of underlying liver disease in many patients with primary liver tumors such as HCC, the tolerance dose of the liver has been shown to be different for patients with primary versus metastatic liver cancers[3]. Thus, evaluation of liver reserve/function is an important aspect of planning liver RT.

The most commonly used classification of liver function is the Child-Pugh score, which accounts for the presence or absence of ascites and encephalopathy and measurements of bilirubin, albumin, and prothrombin, the latter as an international normalized ratio. Although developed in a different context, Child-Pugh score has been used to evaluate patients for RT. In general, patients with Child-Pugh Class A and B7 cirrhosis can safely receive radiation, but patients with Class B8 or above are not considered candidates. Medical management of cirrhosis or other liver disease is always optimized before radiation therapy is begun.

In addition, several imaging modalities allow functional liver assessment. Indocyanin green (ICG) enables assessment of overall hepatic metabolic function and Sulfur colloid Technetium 99m SPECT/CT can define the spatial distribution of functional and cirrhotic liver parenchyma. ICG measurements correlate with development of RILD and mortality[10-12]. Furthermore, subsequent effort showed that ICG measurements can help guide RT: a 5-fraction RT regimen was risk adapted based on ICG measurements at baseline and after 3 initial fractions[13]. Results for 90 patients with HCC and liver metastases showed 2-year local control of 95%, with only an 8% risk of change in CP score > 2[14]. Further work will be needed in patients with larger tumors and more advanced cirrhosis.

While cirrhosis is a major challenge to delivering radiation safely, surgical resection of the liver can reduce hepatic reserve through the removal of functional healthy liver. Although hepatic regenerative capacity can mitigate this problem, large resections can nonetheless substantially limit hepatic reserve. For example, 20%-25% of patients with bilobar liver metastases with planned two-stage hepatectomy cannot undergo the second stage owing to inadequate liver hypertrophy after portal vein embolization and a predicted inadequate liver remnant[15,16]. The role of radiotherapy for patients with small liver remnants (< 1000 cm^3) remains to be defined.

Biliary obstruction often occurs in patients with HCC. Ursodiol is helpful for partial biliary obstruction with stent placement reserved for complete obstruction.

Another aspect of HCC that can directly impact liver function is its predilection to vein invasion. Portal and hepatic venous tumor thrombosis may complicate RT delivery due to liver decompensation caused by the thrombus, the larger radiation volumes needed to cover the thrombus, and the presence of ascites resulting from portal hypertension. Importantly such tumors may represent even a greater management challenge for other local modalities[17]. Studies of radiation alone or in combination with transarterial approaches for tumors with portal vein tumor thrombosis have shown that efficacy of radiation in this setting is not influenced by the location of the tumor thrombus in the same way that transarterial options are and suggested that radiation should be considered in this setting [Figure 1][18-20].

FRACTIONATION

Development of stereotactic ablative radiotherapy (SABR) has revolutionized our approach to patients with liver tumors. Studies of lung[21,22] and liver[23] cancer have shown it to effectively ablate small tumors, defined as local control rates of approximately 90% at 2 years or longer. For these organs consisting of parallel functional subunits, overall organ function depends on preserving a minimum number of these subunits and can otherwise tolerate destructive doses of radiation to small parts of its volume. However, SABR in 3 to 6 fractions is challenging or impossible when the tumors are near critical organs at risk (OARs) whose func-

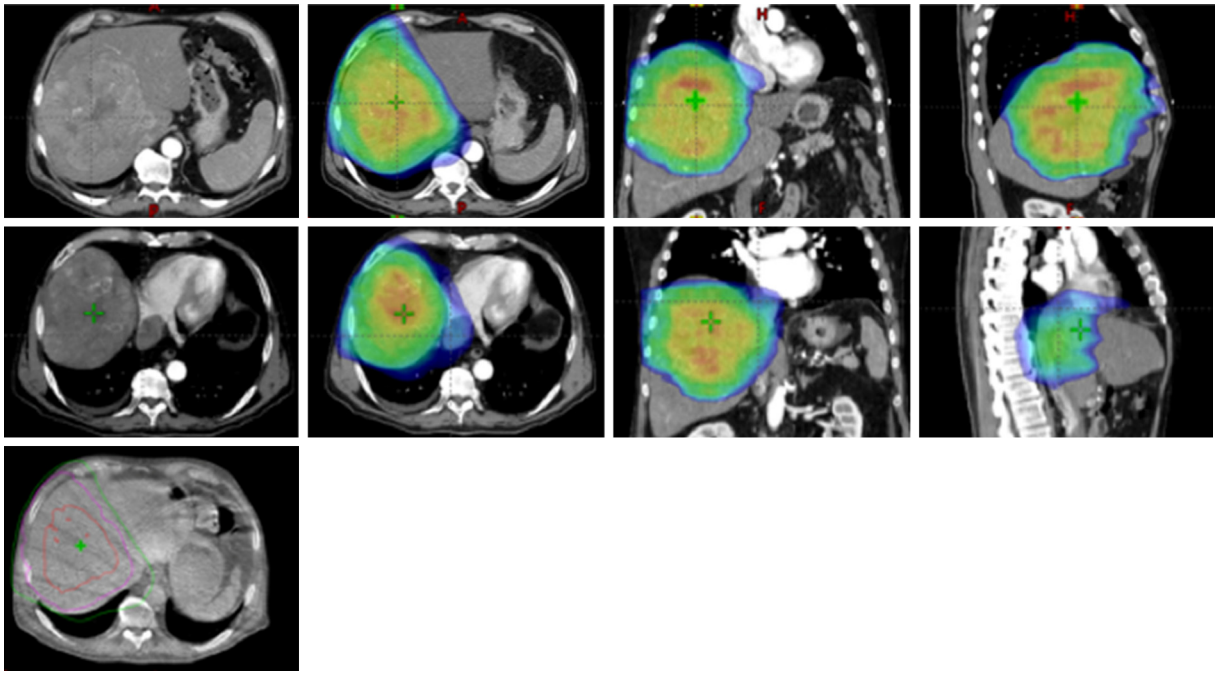

Figure 1. Treatment plan of a patient with an 18-cm hepatocellular carcinoma with extension into the hepatic veins, inferior vena cava and right atrium. Deep inspiration breath-hold was used for motion management. Representative arterial phase images from the simulation computed tomography (CT) are shown in the first column at the level of mid-liver (first row) and at the level of the right atrium (second row), with corresponding dose color wash distributions in all planes immediately to the left. Lowest dose displayed in deep blue is 45 Gy (in 25 fractions) and central hotspot is 75 Gy. Intracardiac extension was treated to 50 Gy. A representative cone beam CT image is shown in the third row

tional subunits are arranged in series, such as the spinal cord and the gastrointestinal (GI) tract or when the tumors are large making it difficult to spare enough liver parenchyma below a certain dose. Typical doses to achieve an ablative effect for HCC given in 3-6 fractions is 54 Gy or biologically equivalent doses (BEDs) of approximately 100 Gy. However, for tumors located near the GI tract these doses cannot be delivered using 3-6 fractions because even a small radiation hotspot can impair organ function. In these cases, the total dose to the tumor is often reduced by 20% to 50% to meet normal tissue constraints, which directly reduces the efficacy of the treatment. Similar dose reductions may be necessary to protect a sufficient amount of liver or to remain within tolerance for the biliary tree[24]. Yet, ablative doses with BED of 100 Gy can be safely delivered to these tumors when a more protracted fractionation is used.

For example, in sequential phase I and II trials of SABR given in 6 fractions to 102 patients with large HCCs with median tumor size 7 cm, the median radiation dose was only 36 Gy in 6 fractions in order to maintain a low risk of RILD. The locoregional control rate at 1 year was good (87%), but inferior to some of the results with protons where more protracted fractionation schemes were used (outlined in a later section), and the rate of grade ≥ 3 toxicity was high (30%) with 7 patients dying of treatment-related causes[25].

These results emphasize that the key to successfully controlling large liver tumors is achieving an ablative dose while staying within tolerance of the organs at risk (OARs), which can often be accomplished by increasing the number of fractions beyond typical 3-6 SABR fractionation schemes [Figure 1].

MOTION MANAGEMENT

Due to the proximity of organs at risk, controlling organ motion is a critical component of treating HCC with ablative radiation. Both intrafraction and interfraction motion need to be considered. Intrafraction

motion is primarily due to respiration (and/or patient movement), while interfraction motion is primarily impacted by the change in location/shape of the liver and luminal organs day-to-day.

The amplitude of liver movement with respiration varies significantly from patient to patient and depends on the location of the tumor within the liver. The range of motion generally is greatest in the cranio-caudal direction, with amplitude exceeding 2 cm in some patients[19]. Further, although breathing amplitudes can be different during four-dimensional computed tomography (4D CT)-based treatment planning versus during radiation delivery, the direction of variability seems to be predictable[20]. With regard to the effect of tumor location within the liver, the closer a tumor is to the center of the hemidiaphragm, the greater the motion. The liver also deforms throughout the respiratory cycle, especially in elderly patients with diminished abdominal wall muscle tone. Chest versus abdominal breathing also affects liver shape, and must remain consistent from the simulation to the treatment delivery. It is important to note that organ motion of the diaphragm is perhaps even more important for proton therapy than for photon therapy because the dose delivery is significantly more affected by tissue density of the surrounding organs in the case of proton therapy.

Intrafraction organ motion due to breathing can either be addressed with respiratory motion control coupled with image guidance or by accounting for the range of motion of the tumor with an internal target volume (ITV). It is often not advisable to use the latter option for liver tumors because of the proximity of organs at risk and the larger normal liver volume that needs to be included. The addition of abdominal compression is an effective way to reduce the ITV. Several commercial devices are available for this application. The most common technique uses an abdominal compression plate that is placed 3 to 4 cm below the costal margin. The plate is connected to a load cell that can measure how much force is being applied to the abdomen. This device is usually used when the superior-inferior movement of the tumor exceeds 1 cm, but it may also be needed for tumors within 1 cm of the GI tract[26]. Because compression plates can cause variable deformation of the liver, an alternative solution for liver tumors is the use of a pneumatic compression belt. This option has been reported to reduce respiratory motion to less than 5 mm[27]. Notably, compression only minimizes rather than eliminates motion, and does necessitate the use of an ITV approach.

Motion management can very efficiently be accomplished with respiratory gating. Options include inspiratory or expiratory breath hold including the Varian RPM system or the Active Breathing Control system. Interfractional variations in breath hold position can exceed 4 mm[28,29], and so a breath hold technique is usually coupled with image guidance to verify the target position with each fraction. Image guidance can be achieved by using 2D image sets or with 3D images obtained in the breath hold position.

Day-to-day differences in bowel position and shape are other uncertainties that must be accounted for and monitored to ensure safe treatment. The extent to which the luminal GI organs affect accurate proton delivery has not been well described and may not be predictable. Filling of the stomach can vary substantially from day to day, depending on the amount of air, liquid, and solid present within it. This variation can lead to an increase in the range of the proton beam, but not the photon beam. This is a relatively minor problem to deal with if during the planning process beams are designed such that they don't traverse the gastrointestinal tract. The left lobe of the liver is susceptible to deformation caused by stomach filing, whereas the right lobe is less affected by the surrounding organs. Generally, we instruct our patients to ingest nothing for at least 3 h before radiation sessions in an attempt to reduce the variability of stomach filling and enhance the tendency of the stomach to pull away from the left lobe of the liver. The amount of solid, liquid and gas in the ascending, transverse, and descending colon can vary from day to day. This variability should be monitored and assessed for position changes near the tumor. We use simethicone for patients who have significant amounts of gas in the large bowel. Reduction in bowel gas can often increase the separation between the tumor and colon.

IMAGE GUIDANCE

As described in the previous paragraphs, image guidance is a critical component of treatment with ablative doses. Some options for image guidance include fiducial-based kilovoltage X-ray solutions that can be used for tumor tracking, deep inspiration breath hold, end inspiration breath hold, and free-breathing gating techniques such as end-expiratory gating and abdominal compression. Another option, soft tissue imaging via CT-on-rails or cone beam CT (CBCT) have the advantage of being able to visualize the interface of the liver with the GI tract, and, most of the time, the tumor within the liver.

Because cone beam CT images are acquired over 40 to 60 s, motion artifact is significant. This can be substantially reduced with a deep inspiration breath hold image acquisition. Most patients can hold their breath for that duration if the image is acquired during deep inspiration. This technique produces images that are clear enough to assess the interface between the stomach and the liver, which can vary from day to day. A gated cone-beam CT is another option but is currently still an emerging technology. For photon therapy, magnetic resonance imaging equipped linear accelerators may offer the best soft tissue definition. This capability will become more widely available in the future.

Most small liver tumors can be treated with a free-breathing ITV that accounts for respiratory motion and setting up to bony landmarks. For larger tumors, or tumors near the GI tract, we recommend a deep inspiration breath-hold technique. Metallic fiducials or surgical clips that have been placed from prior surgery can be used for initial set up. Alternatively, it is possible to use a soft tissue set-up to the liver shape obtained with a breath-hold cone-beam CT.

ROLE OF PROTON BEAM THERAPY

Proton therapy is a form of external beam radiation therapy that utilizes accelerated protons as particles to deliver therapeutic radiation. The benefit of protons derives from the lack of exit dose, resulting in lower integral doses to normal tissues compared to intensity modulated radiation therapy. Theoretically, when using a dosing schema based on meeting a particular mean liver dose threshold, the lack of exit dose may allow for a potentially greater dose of radiation delivered to the tumor. However, the use of protons is also associated with unique challenges that must be taken into account when planning and delivering a treatment.

Proton beam range is highly dependent on the electron density of tissues it transverses. This is one of the reasons for range uncertainty that must be accounted for when creating PTV margins in addition to margins needed for setup uncertainties, and target motion. For liver treatments specifically, the presence of different amounts of air in the luminal organs day to day and diaphragm motion that moves the interphase between lung and soft tissue can significantly impact delivered doses to target and surrounding structures, and must be accounted for when treating with protons. Another important disadvantage of protons is their wider penumbra due to lateral scatter, which results in less conformality. Therefore, PTV coverage for tumors close to the sensitive GI structures is best achieved with IMRT. Dosimetrically the greatest advantage for PBT over photons may in treatment of very large liver tumors with small healthy liver remnants located far from luminal GI tract. NRG-GI003 is a recently opened US multi-institutional phase III trial that randomizes patients with unresectable HCC to photon *vs*. proton based hypofractionated SBRT will determine whether PBT may confer an OS advantage compared to photons. Both a 5 and 15-fraction regimens are allowed at the discretion of the treating physician.

CLINICAL OUTCOME DATA OVERVIEW

Historically, the majority of the ablative radiation therapy experience has come from Japan, where HCC is endemic and quite common. Protons have been largely used as they allowed larger treatment volumes to be treated to larger doses per fraction. Results from hypofractionated regimens (16-25 fractions) to ablative

Table 1. Select studies of proton beam therapy for HCC

Study details			Tumor characteristics				Outcomes				GI toxicity
Study	Fractionation scheme	Number	Median size, cm (range)	Child-Pugh A	Multiple tumors	Prior local therapy	2Y LC	2Y OS	3Y OS	Median survival, months	Grade 3**
Kawashima *et al*.[12]	76 GyE in 20	30	4.5 (2.5-8.2)	67%	10%	37%	96%	66%	62%	41*	6
Mizumoto *et al*.[31]	66 GyE in 10 72.6 GyE in 22 77 GyE in 35	266 104 95 60	3.4 (0.6-13)	76%	53%	63%	(3y) 87%	-	61%	51	6
Bush *et al*.[33]	63 Gy in 15	76	5.5§	30%	14%	-	(5y) 80%†	-	70% (Tx) 10%* (no Tx)	34 (CP A) 13 (CP B) 12 (CP C)	0
Hong *et al*.[32]	67.5 GyE in 15 58.05 GyE in 15	44	5.0 (1.9-12)	79.5%	27.30%	20%	95%	63%	-	50	0
Chadha *et al*.[34]	75.9 Gy in 15	37	5.2	85%	24%	30%	86%	54%	-	25	6

*Estimated from Kaplan-Meier curve; **no grade 4 or 5 toxicity was reported; §mean; †Crude rate. CP: Child-Pugh; LC: local control; OS: overall survival; GI: gastrointestinal; Tx: transplant

doses for large tumors are similar to those after surgical resection, with 5-year local tumor control rates of 90% and overall survival (OS) rates of 50% among some patients[12,30,31].

Representative studies of ablative proton bream therapy for HCC from Japan and early experience in the US are summarized in Table 1[12,31-33]. Several fractionation schemes have been successfully used with higher doses per fraction reserved for peripheral tumors located > 2 cm away from the hilum or sensitive GI structures. Like most studies of patients with HCC, these studies have very heterogeneous inclusion. While overall survival is dependent on patient and tumor characteristics, including liver function, tumor size, multifocality and the presence tumor vascular thrombosis, local tumor control has been in the 90% range when ablative doses have been delivered. Mizumoto *et al*.[31] reported on 266 patients treated with three protocols developed at the Proton Medical Research Center in Tsukuba, including 66 GyE in 10 fractions for tumors > 2 cm away from the portal region, 72.6 GyE in 22 fractions for tumors within 2 cm of the hilum and further reduction to 77 GyE in 35 fractions for tumors adjacent to the GI tract. The majority of the tumors were less than 5 cm. The average 3-year local control and OS were 87% and 61%, respectively. Interestingly, there were no significant differences in local control among the three different fractionation schemes used.

In the US, a recent multi-institutional phase II study of high-dose hypofractionated proton beam therapy for liver tumors included 44 HCC patients with median tumor size of 5.0 cm and tumor vascular thrombosis present in 29.5%. Planned dose was 67.5 GyE in 15 fractions for peripheral tumors and 58.05 GyE in 15 fractions for central tumors. Dose de-escalation was allowed for meeting liver constraints. Median dose delivered was 58 GyE (range 40.5-67.5). LC and OS for this group at 2 years were 94.8% and 63.2%, respectively[32]. Importantly, very few grade 3 toxicities and no grade 4-5 toxicities were observed. Worsening Child-Pugh score (all A to B) was noted in 3.6%.

There are no definitive data on the optimal dose for control of HCC, but collectively these studies suggest that dose escalation above BED of 100 Gy [approximately 80 Gy in 2 Gy equivalents (EQD)] is associated with excellent outcomes and can be safely accomplished using proton beam therapy. Although to date the majority of published experience on the use of ablative doses for large liver tumors requiring 10 or more fractions has been using protons [Table 1], largely due to the greater liver parenchyma sparing they offer over photons, when the same liver constraints are adhered to with photon-based plans using the principles described in this review, the clinical outcomes are similar [Figure 1] (our unpublished data). With greater availability of photon-based therapy and some of the dosimetric advantages IMRT offers over protons, IMRT-

based hypofractionated ablative treatments will most certainly become more frequently used in the future.

In summary, while patients with relatively small, isolated tumors with well-compensated cirrhosis represent ideal candidates for ablative dose escalation, this approach may also be used for select candidates with larger tumors or Child-Pugh class B/C liver disease.

CONCLUSIONS

Radiation therapy is an important local modality for large unresectable HCC. Small tumors can be treated with straight forward approaches that may not require respiratory motion management or soft tissue image guidance. However, large liver tumors are among the most challenging cases to treat with radiation because of the sensitivity of the liver parenchyma, the presence of underlying liver disease, the proximity of the duodenum, colon, stomach, and main bile ducts. Respiratory motion and interfraction motion of the surrounding bowel complicate sparing these organs. These challenges can be overcome by adhering to the following principles which apply to both photon and proton beam therapy. In general, proton therapy spares liver parenchyma better and IMRT spares GI luminal structures better.

(1) Evaluation and optimization of liver function prior to RT. Child-Pugh Class A and B7 are most appropriate candidates for ablative RT.

(2) Selection of fractionation scheme that allows the delivery of ablative radiation doses of 100 Gy BED (80 Gy EQD2) while sparing sensitive normal structures. For most large central tumors, this requires the use of 15-25 fractions with an SBRT technique in order to stay within the tolerance of the OARs.

(3) Respiratory motion management. Breath hold or gating is preferred for large tumors because it minimizes the liver volume that is treated, help to spare the GI tract, and minimizes motion artifact on cone beam images.

(4) Use of soft tissue image guidance. When tumors are located near the GI tract, soft tissue guidance is most important. CBCT allows for verification of the position of the GI tract as well the liver shape.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: all authors

Performed data acquisition, as well as provided administrative, technical, and material support: all authors

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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