

## Liver, Renal, and Retroperitoneal Tumors: Stereotactic Radiotherapy

Brian D. Kavanagh<sup>a</sup> · Tracey E. Schefter<sup>a</sup> · Peter J. Wersäll<sup>b</sup>

<sup>a</sup>University of Colorado Comprehensive Cancer Center, Aurora, Colo., USA;

<sup>b</sup>Karolinska Hospital and Tumor Institute, Stockholm, Sweden

### Abstract

Stereotactic body radiation therapy (SBRT) is currently under active study at numerous centers for clinical application in the management of patients with primary or metastatic tumors of the liver, primary or metastatic tumors of the kidney, and selected other retroperitoneal tumors. Accurate patient positioning and tumor relocalization are essential for SBRT use in the liver and other abdominal and retroperitoneal sites, as at other tumor sites. In a phase I clinical trial at the University of Colorado, patients with liver metastases have received SBRT. Eligible patients had 1–3 discrete liver metastases and no prior radiotherapy to the liver. The aggregate tumor diameter (sum of diameters) was <6 cm. Respiratory control was used. Normal liver volume to be preserved was determined prior to therapy. Dose was prescribed to a planning target volume that included the gross tumor volume plus at least a 5-mm radial and 10-mm superior-inferior margin. SBRT was administered with 6- to 15-MV beams through either dynamic conformal arcs or a combination of multiple noncoplanar static beams. The dose was safely escalated to 60 Gy in 3 fractions. After SBRT to hepatic lesions, it is extremely difficult to radiographically evaluate tumor response within the first few months, and radiographic response analysis may require 4–6 months after SBRT. Care must be taken to avoid focal high-dose therapy to the gastrointestinal mucosa, where the maximum point dose is likely to be the major limitation rather than the mean dose. SBRT has a potential role in the management of renal cell carcinoma, either as an alternative to surgery to the primary site or as cytoreductive therapy directed toward metastatic sites, and in the management of selected retroperitoneal tumors.

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Stereotactic body radiation therapy (SBRT) is a therapeutic option in selected cases of primary or metastatic liver tumors, primary or metastatic kidney cancer, and certain tumors involving other retroperitoneal sites. In each case, there are special technical and clinical considerations to be considered. Here we present an overview of published literature, with a description of key applied concepts and illustrative case studies.

## **Stereotactic Body Radiation Therapy for Liver Tumors**

### *Target Volume Definition and Respiratory Motion Adaptation*

A fundamental issue in all of clinical radiation oncology is the question of whether the perceived target volume to be treated is the true target volume. When non-invasive external beam therapy is guided by noninvasive imaging studies, it is valuable to establish the reliability of the imaging studies in terms of how well they represent the lesion volume and location. Kelsey et al. [1] at the University of Colorado approached this topic for hepatocellular carcinoma (HCC) by means of a clinicopathologic correlative study. For 18 patients with 27 tumors treated surgically for HCC, the preoperative imaging studies were correlated with tumor volume identified on gross pathologic examination. The radiographic and pathologic sizes were closely correlated with either CT or MRI imaging. In most cases (81%), the imaging study overestimated the true gross pathologic size of the HCC. The authors concluded that SBRT utilizing a 0.5- or 1.0-cm margin around the radiographically evident tumor would have encompassed the gross pathologic tumor in 93 and 100% of cases, respectively.

Accurate patient positioning and tumor relocalization are essential for liver SBRT. Dawson et al. [2] reported the setup accuracy of a system of active breathing control supplemented with daily megavoltage imaging for liver SBRT. The average breath-hold time was 12 s. With this combination of techniques, the average motion of the diaphragm during treatment was observed to be less than 1 mm. Fuss et al. [3] at the University of Texas San Antonio used daily ultrasound-based image to reposition patients to upper abdominal target volumes. A combination of adjacent vascular and ductal structures (the portal vein, hepatic artery, bile ducts, aorta, celiac trunk, and superior mesenteric artery) were used as internal reference fiducials to facilitate anatomic localization. The authors found the technique reliable more than 95% of the time, with occasional difficulty resulting from excess gastrointestinal gas that limited visibility. CT scan verification of ultrasound-directed setup guidance confirmed a statistically significant improvement in setup error using this system, with an observed mean magnitude of residual setup error of less than 5 mm.

### *Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma*

Evidence supporting the utility of high-dose, hypofractionated radiation therapy in the management of HCC includes the observations from the University Tsukuba and Loma Linda University involving the application of proton beam treatment. Chiba et al. [4] from Tsukuba reported an experience of 162 patients with medically or surgically inoperable HCC treated by proton beam therapy with or without transarterial embolization and percutaneous ethanol injection. The median total radiation dose was 72 Gy in 16 fractions. The overall survival rate for

all of the 162 patients was 23.5% at 5 years, and the actuarial local control rate at 5 years was 87% for the 192 discrete tumors treated. Adverse prognostic factors in their experience included worse baseline hepatic function and greater number of tumors in the liver. Bush et al. [5] at Loma Linda University reported a similar experience with the use of proton irradiation for patients with unresectable HCC. The total dose given was 63 Gy (calculated as cobalt gray equivalents) in 15 fractions. Among 34 patients with a median follow-up of 20 months, the 2-year actuarial local control and overall survival rates were 75 and 55%, respectively. Subsequent liver transplantation was performed in 6 patients, 2 of whom had no residual carcinoma on histopathologic analysis of the specimen removed.

Regarding the use of photon irradiation, a recently reported French phase II trial assessed the efficacy and tolerance of conventionally fractionated external beam radiotherapy for HCC in cirrhotic patients [6]. A dose of 66 Gy was given to 27 patients with HCC, 15 of whom had previously been treated. Among 23 evaluable patients, nearly 80% (18 patients) experienced a complete response, and another 3 achieved partial response. The experience of Shim et al. [7] was similarly encouraging insofar as it strongly suggested a clinical benefit for conventionally fractionated radiotherapy after transcatheter arterial chemoembolization, a commonly applied therapy.

Among the first group of patients who received SBRT at the Karolinska Institute were 9 patients with HCC and 2 with other primary intrahepatic cancers [8]. Twenty separate tumors were treated in the 11 patients; the doses given ranged from 14 to 45 Gy in 1–3 fractions. Partial or complete response was observed in 60 and 10% of lesions, respectively. Patients commonly developed a low-grade elevation in body temperature and nausea a few hours after treatment, usually prevented with antibiotics. Most patients had only mild symptoms, but 1 patient died 2 days after a single 30-Gy dose to a large HCC in the left lobe of the liver. In an ongoing multicenter prospective pilot trial of SBRT for HCC (H. Cardenes, Indiana University, principal investigator), the initial part of the study is a phase I lead-in to a phase II study. The initial dose cohort was 36 Gy in 3 fractions, and the plan was to escalate the dose by 6 Gy total (2 Gy per fraction) in subsequent cohorts.

#### *Stereotactic Body Radiation Therapy for Liver Metastases*

Herfarth et al. [9] at Heidelberg University reported a phase I/II dose escalation study of single-fraction SBRT for hepatic metastases in which 37 patients participated. The median tumor volume was 10 cm<sup>3</sup> (range, 1–132 cm<sup>3</sup>), and the dose was safely escalated from 14 to 26 Gy in 1 fraction. At the time of that report, the overall actuarial freedom from local failure at 18 months for the entire group was 67%; failures occurred predominantly in patients treated with lower doses. Wulf et al. [10] from the University of Würzburg reported a series that included 23 patients who received SBRT for liver metastases. The typical dose was 30 Gy in 3 fractions.

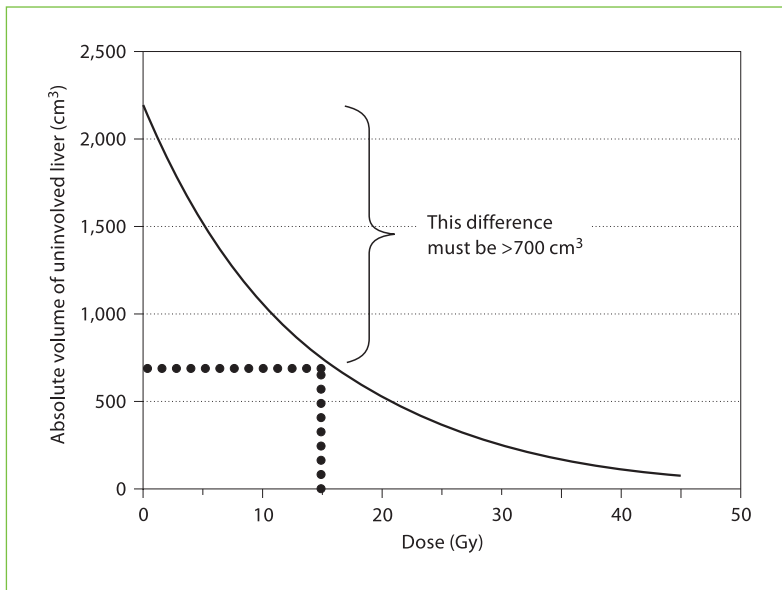
The actuarial rates of local control at 1 and 2 years were 76 and 61%, respectively. There was 1 case of grade 2 hepatitis at 6 weeks, which resolved after steroid treatment. No patient experienced grade 3 or higher toxicity of any kind.

Schefter et al. [11] from the University of Colorado and elsewhere conducted a phase I trial of liver SBRT, electing to use a 3-fraction regimen. Eligible patients had 1–3 discrete liver metastases, had had no prior radiotherapy to the liver, and had not had any chemotherapy for at least 2 weeks prior to SBRT. The aggregate tumor diameter (sum of all maximum individual tumor diameters) had to be less than 6 cm. The dose was escalated according to a standard 3 + 3 phase I study design. The first cohort received 36 Gy in 3 fractions (12 Gy/fraction), and for subsequent cohorts the total dose was increased by 6 Gy (2 Gy/fraction). Dose-limiting toxicity was defined as any grade 3 liver, gastric, small bowel, or spinal cord toxicity or any grade 4 toxicity from SBRT. It was preordained within the protocol that the maximum dose escalation would be to a total dose of 60 Gy in 3 fractions, even if the maximum tolerated dose had not yet been reached.

Dose was prescribed to a planning target volume (PTV) that included the gross tumor volume (GTV) plus at least a 5-mm radial and 10-mm superior-inferior margin. Respiratory control (abdominal compression or a breathing coordinator) was used. SBRT was administered with 6- to 15-MV beams through either dynamic conformal arcs or a combination of multiple noncoplanar static beams. The 3 fractions of SBRT could be given on consecutive or nonconsecutive days within a 2-week span. Prophylactic antiemetics were allowed at the discretion of the treating radiation oncologist.

A simplified form of the ‘critical volume’ model, initially proposed by Yaes and Kalend [12], was applied to construct the normal liver dose restriction in the University of Colorado trial. The essence of this model is that for a given irradiated organ, it is necessary to preserve a minimum ‘critical volume’ of cells with the capacity to regenerate so that organ function can be preserved. Based upon literature regarding surgical resection, it was estimated that if a ‘critical volume’ in the range of 500–600 cm<sup>3</sup> of normal liver were preserved, there should be adequate reserve to allow repopulation and maintenance of normal liver function.

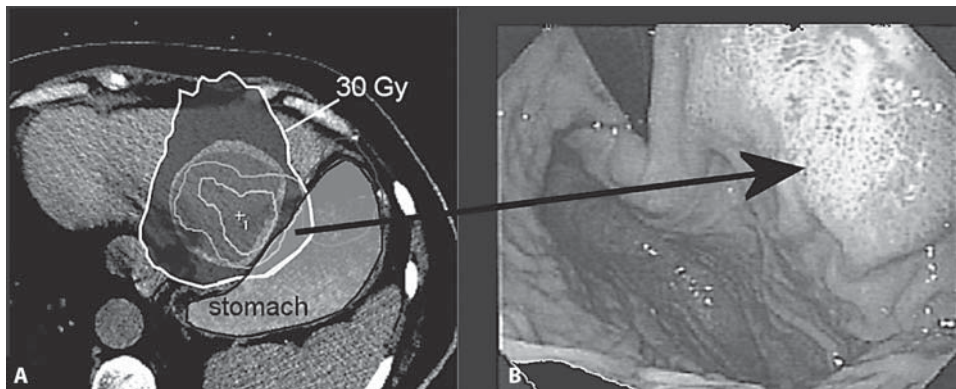
It was also known from prior studies of whole-liver radiotherapy that a dose of 30 Gy in 20 fractions was expected to be well tolerated [13]. If an alpha/beta ratio of 3 is assumed, the biologically equivalent dose (BED) of this regimen may then be calculated as 45 Gy<sub>3</sub>. Therefore, it was hypothesized that if an extraconservative ‘critical volume’ of at least 700 cm<sup>3</sup> of normal liver received a BED of less than 45 Gy<sub>3</sub>, adequate reserve capacity should be preserved. Additional caution was applied in restricting the dose to the 700-cm<sup>3</sup> ‘critical volume’ to a maximum of 15 Gy in 3 fractions, which yields a BED of 40 Gy<sub>3</sub>. The use of dose-volume histogram (DVH) information to assess compliance with a critical volume-type restriction has not been commonly done in the past (an illustrative example is provided in fig. 1).



**Fig. 1.** Representative normal liver DVH, with indicated critical volume restriction whereby no more than 700 cm<sup>3</sup> may receive more than 15 Gy. The horizontal and vertical dotted lines converge upon the point on the curve indicating the volume of normal liver that receives 15 Gy or more; thus, the difference between the total normal liver volume and the volume receiving 15 Gy or more, here indicated by a brace, must be more than 700 cm<sup>3</sup>.

Eighteen patients participated in the University of Colorado phase I liver SBRT study. A trend of asymptomatic elevation in serum liver enzymes was noted within the first few months after SBRT, but no patient experienced a dose-limiting toxicity. The dose was therefore safely escalated to 60 Gy in 3 fractions. Typically, well-defined regions of hypodensity in the normal liver tissue around the GTV were observed on CT scans obtained within the first few months after SBRT, similar to what has been reported after single-fraction SBRT [14]. The etiology of this phenomenon is not yet completely understood; a lymphocyte-mediated mechanism has been hypothesized [11]. Regardless of the mechanism, the important clinical relevance is that it is extremely difficult to evaluate tumor response within the first few months radiographically on account of this effect. Therefore, in clinical trials of liver SBRT in which tumor response is a primary endpoint, it is advisable to set the time point of radiographic response analysis at least 4–6 months after SBRT.

It should be appreciated that observations of the tolerance of normal liver to SBRT cannot be converted into assumptions regarding the tolerance of the gastrointestinal tract mucosa, generally assumed to be constructed in radiobiologically serial architecture, where the maximum point dose is the major



**Fig. 2.** **A** Cross section from the case study planning CT scan showing the 30 Gy isodose contour (thick white line) overlapping the stomach (labeled, outlined in black, and shaded in transparent gray). Other contours represent the GTV and PTV, and higher isodose contours are shaded regions inside the 30-Gy contour. **B** Image from an upper endoscopy approximately 8 weeks after liver SBRT. The arrowhead indicates an area of pale, denuded mucosa within the region that received more than 30 Gy.

limitation rather than the mean dose. It is likewise not known whether there is an equivalent application of critical volume-type dose constraints that would be appropriate, as seems to be the case for liver tissue. The following case study is illustrative.

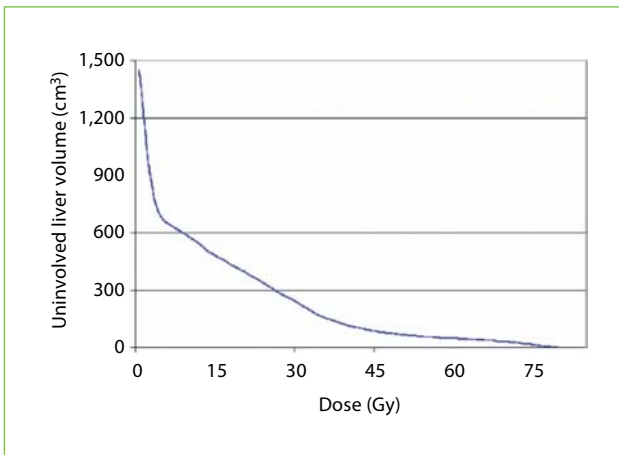
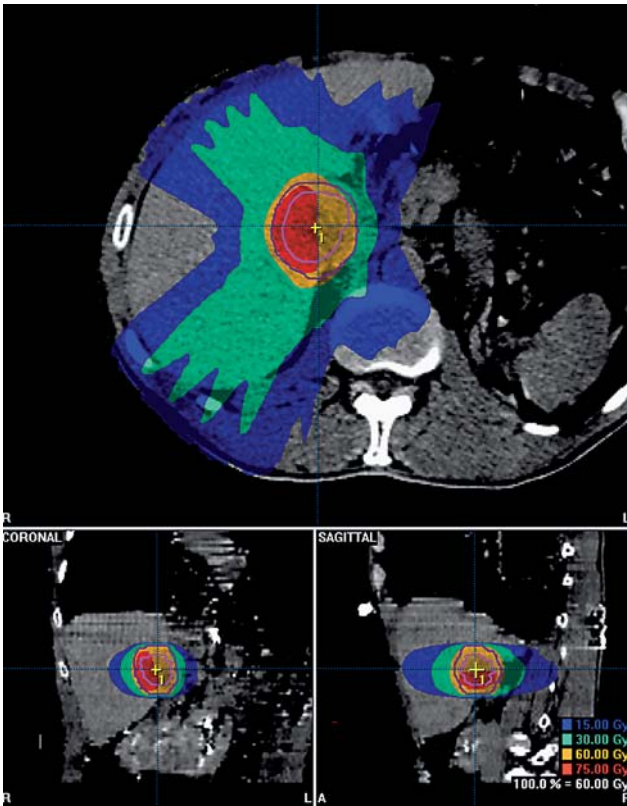
#### *Case Study 1*

##### *Stereotactic Body Radiation Therapy Tolerance Dose in the Gastrointestinal Mucosa*

A 64-year-old female with metastatic colon cancer who had initially been treated with SBRT to lesions in the lung more than 2 years previously developed a new liver metastasis and was evaluated as a candidate for the phase I liver SBRT study. However, after a planning CT scan was obtained, it was evident that it would not be possible to treat her to the full prescription dose of the available cohort (54 Gy in 3 fractions) without exceeding the maximum point dose allowed by the protocol to gastrointestinal mucosa, i.e. 30 Gy in 3 fractions. Nevertheless, in an effort to give aggressive therapy to the patient who had had a generally favorable clinical course, the liver PTV was treated to a dose of 45 Gy in 3 fractions despite the inclusion of a section of the medial stomach within an isodose volume that received more than 30 Gy (fig. 2A).

The patient complained of dyspepsia within a month after treatment. Despite medical therapy with antacids, the discomfort persisted and worsened to pain requiring narcotic analgesics. Approximately 8 weeks after SBRT, an upper endoscopy revealed a region of pale mucosa that appeared to be poorly vascularized (fig. 2B). Proton pump inhibitor therapy was then added. Within 1 more month, repeat endoscopy revealed that the lesion had progressed to a shallow ulceration. Within another 2 months, the lesion gradually healed and symptoms abated with continued medical management.

It is possible that if an endoscopy had been performed earlier, initially the changes would have resembled a straightforward mucositis, with redness progressing to a pseudomembranous covering. However, the observed endoscopic changes were strongly suggestive of devas-



**Fig. 3.** Case study showing axial, coronal, and sagittal views of the isodose distribution superimposed on CT images. Also, the DVH of uninvolved liver is shown.