

Stereotactic Body Radiation Therapy for Liver Metastases: Single Institution Experience

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Abstract

Background: Stereotactic body radiation therapy (SBRT) is an emerging local treatment for limited liver metastases. We report a single institution experience with liver metastases treated with SBRT.

Methods: Twenty-three consecutive patients treated with SBRT for 27 liver metastases: eight women and 15 men, median age 69 years (26 to 87). SBRT was the chosen therapy when the disease was considered life-limiting and unsuitable for resection or radio-frequency ablation. The median radiation dose was 40 Gy (20 to 50 Gy) delivered in one to 10 fractions. Response to treatment was measured according to RECIST criteria on post-treatment CT, MRI and/or PET imaging. Acute and late toxicities were graded according to CTCAE v4.0.

Results: Twenty-two patients completed SBRT. One stopped treatment after three fractions due to biliary obstruction from progressive tumor. Treatment was well-tolerated, with three patients (13.6%) presenting with Grade 1 and two (9%) presenting with Grade 2 acute gastrointestinal toxicity. Median follow-up was 15 months (range: 3-43) with one patient lost to follow-up. A single patient had symptomatic colitis that resolved with conservative treatment. Complete response was initially achieved in eight of 25 (32%) lesions, partial response in four (16%), disease stabilization in 12 (48%), and continued progression in one (4%). At last follow-up, six of 21 patients (28.6%) had progression of a treated lesion. Actuarial overall one-year and two-year survival rates were 94% and 60%, respectively (median 30.1 months). Actuarial one and two-year local control rates were 62%.

Conclusions: SBRT is a promising well-tolerated treatment for non-resectable liver metastases.

Categories: Internal Medicine, Radiation Oncology

Keywords: liver metastases, stereotactic body radiation therapy, sbrt

Introduction

The liver is a common site of metastatic disease. Hepatic involvement can lead to serious morbidity and is often life-limiting. Approximately half of metastatic death from breast and prostate cancers are associated with liver metastases. Death due to colorectal cancer is commonly related to liver metastases, often the only site of metastatic disease.

When liver involvement is limited, aggressive local treatment is a therapeutic option that can lead to long-term disease control [1-4].

For many primary tumors sites, systemic therapy may allow for transitory responses and increased median survival. Infrequently utilized, palliative whole liver radiotherapy may offer some symptomatic relief [5]. Surgical resection of hepatic metastasis, typically for colorectal cancers, can lead to five year overall survival rates of up to 58% [6]. Nonetheless, clinical and technical limitations narrow eligibility to metastasectomy. Limitations may relate to: intra-hepatic location of the metastases, surgical plans which would not spare sufficient healthy liver, medical co-morbidities, and patient refusal. Only about 10 to 25% of patients with liver metastases from colorectal cancer can benefit from curative resection [7-8].

Nowadays, new therapeutic options have been developed for the remaining patients, enabling radical treatment without or in combination with surgery: microwave ablation, radiofrequency ablation (RFA), and stereotactic body radiation therapy (SBRT).

RFA is limited to lesions measuring less than 4-5 cm. Radiofrequency is generally avoided for lesions adjacent to large vessels and those sub-capsular locations. Treatment of anatomically unfavourable lesions could lead to a tumor-sparing heat sink effect and/or a risk of thermal injury to vessels, biliary structures or adjacent organs. Major complications are seen in about 5% of the patients after RFA: portal thrombosis, hemoperitoneum, colic perforation, seeding of the catheter trajectory or hepatic abscess.

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Radiotherapy for liver metastasis was originally limited by radiation-induced liver disease (RILD), which occurred with therapeutic doses of whole-liver irradiation. Liver tolerance to radiotherapy depends on treatment volume and fractionation. In standard fractionation, severe RILD occurs with increasing frequency at whole-liver doses of ≥ 36 Gy, and is much rarer with mean doses inferior to 31 Gy. An analysis of over 200 patients with hepatic tumors treated at University of Michigan demonstrated that much higher doses of radiation can be delivered to a small volume of liver. For irradiated volumes below 25% of the liver, a high dose (>100 Gy in standard fractions) can be given with a low risk of RILD [9]. Patients with liver metastases are less prone to have underlying liver disease as is often the case of patients with primary liver tumors. They are thus more tolerant of liver-directed therapies.

SBRT allows delivery of high doses per fraction to small volumes with geographic sparing of adjacent organs at risk. Published series of SBRT for liver metastases report median survival time of six months to 4.3 years, with actuarial local control at one to two years, ranging from 67 to 92% [10-14].

In the present review, we report a single institution's experience with liver metastases treated with SBRT.

Materials And Methods

Patients

A multidisciplinary tumor board composed of surgeons, radiation oncologists and medical oncologists reviewed cases and made recommendation for systemic and liver-directed therapies. Stereotactic body radiotherapy was the preferred treatment when the disease was considered life-limiting and unsuitable for resection or radio-frequency ablation.

Patients were considered for SBRT when they had a limited number of lesions (≤ 3 lesions) and 700 cc of liver could be spared. Extrahepatic disease did not per se exclude patients from SBRT. Through review of the radiation-oncology SBRT database, 23 consecutive patients were identified. These patients were treated with SBRT for 27 liver metastases from November 2006 to September 2010. Clinical information was collected retrospectively from the electronic charts of the patients at McGill University. All patients gave informed consent for their treatment.

Patients had a median age of 69 (range: 26 to 87) at the time of SBRT. There were eight women and 15 men.

Nine (39%) patients had extra-hepatic metastatic disease, and 14 (61%) had been previously treated with chemotherapy. One to three lesions (median one lesion) were treated in each patient. Table 1 shows patient characteristics.

Characteristic	Patients, n=23
Age, years	Median 69 (26 - 87)
Sex F:M	8:15
Primary site	
Colon	12 (52.2%)
Rectum	2 (8.7%)
Breast	1 (4.3%)
Gastric	1 (4.3%)
Nasopharynx	1 (4.3%)
Pancreas	1 (4.3%)
Bladder	1 (4.3%)
Leiomyosarcoma	1 (4.3%)
Prostate	1 (4.3%)
Endometrium	1 (4.3%)
Ovary	1 (4.3%)
Number of Lesions	
1	21 (91,3%)
3	2 (8.7%)
Lesion Dimension	Mean 3.2cm (0.7 - 10.6
Dose, Gy	Median 40 Gy (20 - 50)
Dose per fraction, Gy	Median 6 Gy (3 - 20)
Number of fractions	
1	1 (4.3%)
3	6 (26%)
4	2 (8.7%)
5	1 (4.3%)
6	2 (8.7%)
10	11 (47.8%)
Previous chemotherapy	14 (61%)
Extra-hepatic metastases	9 (39%)

TABLE 1: Patient Characteristics

Radiation treatments

Twenty patients (24 lesions) received SBRT from a conventional linear accelerator (Linac), and three (three lesions) were treated with the CyberKnife radiosurgery system (Accuray, Sunnyvale, CA).

Fiducials for daily image-guided radiotherapy (IGRT) were implanted percutaneously in peripheral intratumoral locations with computed tomography (CT) (22 patients) or ultrasound (one patient) guidance. One to four fiducials were placed in each liver [15].

Patients were either immobilised with a double-vacuum cushion system or a simple vacuum cushion. Three

and four dimensional simulation images were co-registered, when possible, to diagnostic MRI or CT images. Gross tumor volume (GTV) was expanded by 0-5 mm to for a clinical target volume (CTV). An additional 3-7 mm were added to produce planning target volume (PTV). Four to 10 fields were used for isocentric Linac planning, whereas 59 to 129 beams were used for in CyberKnife cases. The median radiation dose was 40 Gy (20 to 50 Gy) delivered in one to 10 fractions. Seven (30%) patients were enrolled in a multi-institutional clinical trial. Treatments were delivered with respiratory gating, so-called adaptive gating (ExacTrac, BrainLab, Feldkirchen, Germany) or predictive tumor tracking.

Patients were monitored for in-field and out-of-field local recurrences, as well as extra-hepatic recurrences with CT, magnetic resonance imaging (MRI), and/or positron-emission tomography (PET). Overall survival was also calculated on an actuarial basis.

Initial response to treatment was measured according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria three to six months after SBRT. Local progression was defined as an increase of at least 20% in a treated lesion. Time to local progression was measured from the first day of SBRT. For survival, patients were censored at the time of last contact.

Acute and late toxicities were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicity was defined as events occurring within the first three months after SBRT.

Statistics

GraphPad Prism® version 5.0 for Windows (GraphPad Software, San Diego, CA) was used to calculate and chart actuarial survival and local control results.

Results

Out of the 23 initial patients, 22 completed the SBRT treatment, making for 26 lesions, measuring 0.7 to 10.6 cm (median 3.2 cm). One patient with gastric cancer stopped treatment after three fractions due to biliary obstruction from progressive tumor. Fourteen patients (63.6%), with 16 lesions had colorectal cancer.

Median GTV volume was 10.65 mL (0.6 to 312.5 mL), and median contoured liver volume was 1497 mL (938 to 3400 mL).

Treatment was well-tolerated, with no RILD or serious liver toxicity observed. Three (13.6%) patients had Grade 1 acute toxicity (right upper quadrant discomfort in three patients) and two (9%) had Grade 2 toxicity – one with diarrhoea and another with both nausea and vomiting. As for late toxicity, a single patient had symptomatic colitis (Grade 2), which resolved with conservative treatment.

With one patient lost to follow-up, 21 patients with 25 lesions were followed for a median of 15 months (range: 3-43 months).

Complete response was initially achieved in eight of 25 (32%) lesions, partial response in four (16%), disease stabilization in 12 (48%), and continued progression in one (4%).

At last follow-up, six of 21 patients (28.6%) had progression of a treated lesion, and the one and two year local control rate was 62% (Figure 1).

Actuarial overall one year and two year survival rates were 94% and 60%, respectively (Figure 1) (median 30.1 months). Overall survival was not significantly different between patients with colorectal vs. other primary malignancies.

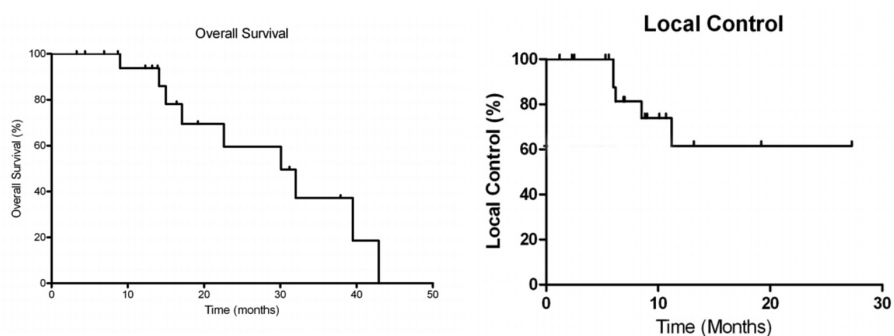


FIGURE 1: Overall Survival and Local Control

The graphics illustrate actuarial overall survival and local control for our study population.

Discussion

This retrospective study corroborates the safety of SBRT in the treatment of liver metastases not suitable for surgery or radiofrequency ablation. As with other SBRT studies [14, 16-17], treatment was generally well-tolerated, with mild acute toxicity and a low Grade 2 or higher late toxicity incidence in this series. Despite treatment of large lesions, only a single patient (4.5%) developed significant late toxicity in the form of symptomatic colitis which resolved with conservative treatment. Reduced treatment volumes through the use of fiducials, tracking, and adaptative gating may have contributed to reducing toxicity. As the dose-limiting organ(s) vary from case to case, the number of patients treated is still insufficient to fully describe the tolerance of the adjacent organs to high dose delivered to small volumes. Likewise, liver tolerance using hypofractionation is not well understood. Given the low symptomatic hepatotoxicity seen in our study and in the literature, there might be room for escalation in normal tissue tolerance levels [17].

In the last few years, advances in systemic therapy have resulted in a better prognostic for patients with metastatic colorectal cancer, with median survivals reaching two years [18]. For the patients with limited liver metastatic disease amenable to surgical resection, five year survival can reach up to 43% [19-21], thus demonstrating the importance of an aggressive local treatment approach. In complement to surgery, microwave ablation, and RFA, SBRT is becoming an increasingly used local therapy, applying the principles of radiosurgery, widely used for brain tumors, to tumors outside the brain.

Different liver SBRT studies report local control rates ranging from 55 to 97% at one to to years [9, 13-14, 16-17, 22]. This wide range can be due to patient, treatment and follow-up heterogeneity across studies.

In our study, with a wide range of histologies and fractionation, a local control rate of 62% at two years was calculated. It is within but on the lower side of the range of reported series. This may be explained by the varied histologies and the different tumor number and sizes treated (some of the lesions were larger than typical in most studies). Another factor may be the total dose, lower than in some other reports – median radiation dose was 40 Gy (20 to 50 Gy) – and dose per fraction. Several of the patients were treated in a Phase I trial which used conservative dosing schemes as a starting point for escalation. Chang, et al. demonstrated that local control for colorectal metastases is dose-dependent, with 18-month local control diminishing from 84 to 43% when total dose was under 42 Gy [17].

The impact of SBRT on survival is not yet determined [17]. Upcoming years may see prospective comparisons to other local modalities and evaluation of SBRT in the treatment of oligometastatic disease in cancers where this is not yet a widespread standard (small cell lung, for example). Many factors will influence overall survival, including active extra-hepatic disease. Extra-hepatic disease has shown to correlate with worse survival in other surgical [18, 23] and SBRT [17] series. Actuarial survival at one to two years with SBRT for liver metastases has been reported in the literature to range from 71-94% and 30-62%, respectively [24].

In our population, with 39% of the patients having active extra-hepatic disease, actuarial one and two year survival rates were 94 and 60%, respectively, which is in agreement with the published literature. Our patient numbers are too small to reliably tease out prognostic factors.

Conclusions

Our series contributes to a growing literature indicating that SBRT is a feasible, safe and effective treatment for selected liver metastases.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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