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Research Article

Stereotactic Body Radiation Therapy (SBRT) for Liver Metastasis: Early Experience with the Cyberknife Robotic Radio-Surgery System

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Abstract

Background: The liver is a common site for malignant metastases. Surgical metastatic resection, ablative therapies, and external beam radiation therapy (EBRT) all have advantages and limitations. Preliminary reports reveal SBRT treats hepatic metastases with limited toxicities. We reviewed our institution's SBRT experience for the treatment of liver metastases to assess toxicity and outcomes.

Methods: Hepatic metastases treated with SBRT were retrospectively reviewed from 2008-2010. Computed tomography (CT) identified tumor volume prior to SBRT, local recurrence and out-of-field progression after SBRT. Study endpoints were local recurrence, toxicity, and overall survival.

Results: Thirty-three patients had 37 liver metastases treated with a median SBRT dose of 30Gy. Median follow-up was 8.1 months. Five lesions (13.5%) locally recurred after a median of 10.6 months. Seventeen patients had out-of-field progression (15 liver, 6 systemic) after a median of 5.1 months. Overall 23.5-month survival was 45.5%. Five patients reported nausea and seven reported pain after SBRT. There were no grade 4-5 toxicities or cases of liver failure.

Conclusion: SBRT is safe and well tolerated in patients with hepatic metastases. SBRT offers a local therapy with limited toxicities to patients with lesions not amenable to traditional ablative, surgical, or regional therapies.

Keywords: Hepatic; Liver; Metastasis; Cancer; Stereotactic body radiation therapy (SBRT); Cyberknife

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Introduction

The liver is a common site of metastasis for many tumors, especially from the gastrointestinal tract. Select patients with isolated liver metastases may benefit from aggressive therapy including surgical resection of hepatic disease [1-4]. Five-year survival rates of patients after hepatic metastatic surgical resection are 30-40% in colorectal cancer [4, 5]. Five-year survival rates for select patients treated with surgical resection for liver metastases are 20-33% in breast cancer [6, 7] and 9-38% in ovarian cancer [8,9]. While hepatic metastectomy has lengthened survival and cured select patients, the majority of patients are not candidates for surgical resection [10, 11]. In colorectal cancer, less than 20% of patients are candidates for surgical resection [12].

While surgical resection of hepatic metastases is the preferred method of treatment, the management of patients with unresectable hepatic lesions is less well defined and multiple opinions exist. Non-resectional therapies including cryotherapy, microwave ablation, and radiofrequency ablation have been developed to treat patients with hepatic metastatic disease not amenable to surgical resection [13]. These modalities have demonstrated some success improving local recurrence and hold potential for prolonged survival. Cryotherapy has been shown to have a 12-39% local recurrence rate and a 17% five-year survival rate [13-16]. Microwave ablation is associated with a 5-13% local recurrence rate and a 16% five-year survival rate [13, 17, 18]. Studies on radiofrequency ablation report a 10-31% local recurrence rate and a 24% five-year survival rate [13, 19-21]. Prior literature has found higher local recurrence rates and higher rates of morbidity for larger hepatic lesions treated with ablative techniques [22-26]. Additionally, there are limitations to ablative therapy when the metastasis is centrally located [22]. Advantages of these therapies include hepatic parenchymal preservation, less physiological stress, and less invasive strategies [13]. While ablative therapies may alter the natural history of these cancers, the overall five-year survival rate remains less than 25% for all three modalities likely secondary to the advanced nature of disease in the patients treated [13].

External beam radiation therapy (EBRT) directed at liver metastases has had limited success with a high local recurrence rate, poor survival rate, and toxicities [27-29]. Normal hepatocytes are sensitive to radiation doses above 35 Gy [28, 29]. EBRT is associated with significant damage to surrounding healthy liver parenchyma when attempting to deliver effective radiation doses to the tumor, therefore limiting therapeutic doses to the cancer [20, 30]. Three-dimensional conformal radiotherapy has made it possible to deliver higher doses of radiation to a specified hepatic location without increasing the dose to the surrounding liver volume [31]. However patients with radiation-induced liver disease, who received higher doses of 3-D radiotherapy, had a significantly higher probability of normal tissue complications [32, 33].

Stereotactic body radiation therapy (SBRT) addresses the limitations of conventional radiation (EBRT) when treating liver metastases [34-36]. SBRT is robotic radiosurgery that delivers radiation via a linear accelerator mounted on a robotic arm that tracks and ablates the metastatic target in real time. As opposed to conventional EBRT, SBRT uses improved immobilization and tracking in order to deliver high doses of radiation with high degrees of precision; fiducial markers are placed in or near the target lesion to account for respiratory motion [34]. SBRT has been utilized to treat cancer in many other sites aside from the liver. The higher doses delivered by SBRT (up to 40 Gy per fraction) compared to conventional EBRT (2 Gy per fraction) result in more efficient cell kill while improving targeting and allowing for less radiation delivered to nearby normal tissue. This allows for delivery of high dose radiation to the metastatic lesion

and a minimal dose to surrounding tissues [37, 38].

Radiation is delivered based on the biological effective dose (BED), which is a mathematical concept used to translate the improved efficiency (decreased ability for DNA repair) seen with higher doses of radiation given in smaller numbers of fractions. For example, 60 Gy in three 20 Gy fractions is the equivalent of 75 fractions of 2 Gy per fraction given every day using the BED equation: BED (2 Gy equivalent) = dose * fractions (dose+10) / (12) where we use an alpha/beta ratio of 10 (conventional for tumors).

With the development of SBRT, metastatic liver lesions can be treated with therapeutic radiation doses without traditional toxicity, therefore this therapy may benefit patients that are not candidates for traditional surgical resection of liver metastases. The goal of this study was to review our institution's early experience with SBRT to treat liver metastases in patients whose lesions were not amenable to surgical resection or were considered poor surgical candidates to determine if SBRT can effectively treat these patients with limited toxicity.

Methods

We conducted a retrospective review of an IRB approved prospective database to assess the outcomes of patients treated at our institution with SBRT for liver metastases. Inclusion criteria were all patients treated with SBRT for liver metastasis from June 2008 to June 2010. Metastatic lesions were included from any location within the liver. All included patients were discussed at multi-disciplinary tumor conference. Patients selected for treatment with SBRT were not considered candidates for surgical resection secondary to tumor location, comorbidities, clinical presentation, or extent of disease.

The patients in this study received SBRT by the Cyberknife® Robotic Radiosurgery System (Accuray, Sunnyvale, California). It is an image-guided SBRT system that uses a linear accelerator mounted on a robotic arm with a respiratory compensation system called Synchrony® Respiratory Tracking System (Accuray, Sunnyvale, California) to guide the robot in applying radiation to the targeted lesion [39]. Pre-treatment imaging using computed tomography (CT) and MRI were used to identify the gross tumor volume. All patients had fiducials placed to mark the location of the metastases and account for respiratory motion. Treatment planning, length of treatment, and radiation doses were determined by the radiation oncologist overseeing treatments.

Following SBRT therapy, repeat CT scans and laboratory blood work were completed to identify treatment response. An attending radiologist reviewed these CT scans to evaluate local tumor control, one of our primary study endpoints. Increased enhancement or tumor progression within the SBRT treatment field on follow up CT scan indicated in-field local tumor recurrence. Out of SBRT field hepatic recurrences were defined as regional recurrence and extrahepatic recurrence was defined as systemic progression. Both regional recurrence and systemic progression were also monitored via follow up CT scans. A Kaplan-Meier curve was used to evaluate local control rates and actuarial survival.

Medical records were reviewed to collect patient demographic data including age and sex. Tumor characteristics analyzed included tumor primary, TNM staging, number of liver metastases, size and location of liver metastases, and presence of extra-hepatic metastasis. Prior treatments for their primary malignancies including surgery, chemotherapy, and radiation therapy were recorded.

The primary study endpoints were local tumor control, survival, and toxicity secondary to SBRT. Toxicities evaluated included nausea, emesis, post-therapy pain, and liver failure. The Common

Terminology Criteria for Adverse Events (CTCAE) was used to define toxicity grade following SBRT for liver metastases.

Fisher's Exact Test, two-tailed Student's t-Test, and Wilcoxon Rank Sum Test and were used to compare categorical and continuous variables. A p-value ≤ 0.05 was considered statistically significant.

Table 1 Clinical Characteristics of all Patients (n=33) Prior to SBRT for Liver Metastases (n=37)

Age (years)	58.3 (27.9-85.3)*
Gender (male)	16 (48.5%)
Time from Diagnosis to SBRT (months)	33.3 (5.7-320)
Time from Metastases Diagnosis to SBRT (months)	13.5 (1.6-109)
Hepatic Lobe (Right)	28 (75.7%)
Tumor Diameter (cm)	4.0 (1.6-13.9)
Number of Hepatic Metastases	3 (1-5)
Multiple Hepatic Metastases	16 (48.5%)
Prior Primary Surgical Resection	27 (81.1%)
Prior Chemotherapy	26 (78.8%)
Prior Radiation	15 (45.5%)
* Median (Range)	

Results

Clinical Characteristics of All Patients Prior to SBRT (Table 1)

Thirty-three patients had 37 liver metastases treated with SBRT between June 2008 and June 2010 in the first 2 years of experience at our institution using SBRT. Clinical characteristics of the patients treated with SBRT for liver metastases prior to therapy are reported in Table 1. Our patient population was 48.5% male (16 males, 17 females) with a median age of 58.3 (27.9-85.3) years old at the time of SBRT. Of the treated metastases, 28 were located in the right lobe and 9 in the left lobe. The median diameter of the metastatic liver lesions was 4.0cm (1.6 to 13.9 cm). Twenty-nine patients (87.9%) were treated for solitary hepatic metastatic lesions and four patients (12.1%) were treated for two hepatic metastatic lesions with SBRT. Sixteen of 33 patients (48.5%) had multiple liver metastases. There was a median of 3 hepatic metastases (1-5 hepatic metastases) per patient and 1.3 ± 0.8 metastases were treated with SBRT. A median time period from diagnosis of primary cancer to SBRT was 33.3 months (5.7-320 months). A median of 13.5 months (1.6-109 months) had elapsed between the diagnosis of liver metastases and SBRT. Colorectal cancer was the predominant primary tumor type identified in 39.4% of patients (13 patients). The remaining tumor primaries were varied and included 4 ovarian, 4 breast, 3 melanoma, 2 liver, 2 lung, 1 gastric, 1 cholangiocarcinoma, 1 pancreas, 1 anal, and 1 bladder.

Prior to SBRT, the majority of patients (27 of 33, 81.8%) had undergone surgical resection of their primary tumor and chemotherapy for treatment of metastatic disease (26 of 33, 78.8%). Additionally, 15

of 33 patients (45.5%) had radiation therapy to their primary tumor site prior to undergoing SBRT for liver metastases. Fifteen patients (45.5%) had extra-hepatic disease located in the lung (4, 26.7%), colon (3, 20%), mediastinum (2, 13.3%), spine (2, 13.3%), orbit (1, 6.7%), bone (1, 6.7%), pharynx (1, 6.7%), and retroperitoneum (1, 6.7%).

SBRT treatments were given over a median of 5 days (3-17 days). The 33 patients with hepatic metastases received 3-6 treatments of SBRT. Patients were treated with a median fraction dose of 10 Gy with a range from 4.5 to 14 Gy. The median total radiation dose provided to patients was 30 Gy with a range of 22.5-42 Gy. Patients either received 3 (81.1%) or 5 (18.9%) fractionations. The median BED was 50 Gy (range 27-84 Gy).

Table 2 Clinical Characteristics of Patients with Local Recurrence vs No Recurrence

	Local Recurrence within SBRT Field (n=5)	No Recurrence (n=9)
Age (years)	59.5 (33.6-73.3)*	58.3 (44.8-82.3)
Gender (male)	1 (20%)	5 (55.6%)
Time from Diagnosis to SBRT (months)	17.6 (14.3-49.6)	47.3 (6.3-205.0)
Time from Metastases Diagnosis to SBRT (months)	14.3 (4.3-29.7)	18.6 (4.3-109.0)
Follow Up Length (months)	10.6 (1.7-19.7)	4.7 (1.2-23.5)
Prior Primary Surgical Resection	4 (80%)	9 (100%)
Prior Chemotherapy	4 (80%)	7 (77.8%)
Prior Radiation	2 (40%)	3 (33.3%)
Tumor Diameter (cm)	4 (1.5-13.9)	3 (1.5-5.3)
Radiation Dose (Gy)	28.5 (25-36)	30 (25-36)
Fraction Dose (Gy)	9.5 (5-12)	10 (5-12)
Number of Fractions (3, 5)	3 (60%)	6 (66.7%)
	2 (40%)	3 (33.3%)

*Median (Range)

Local In SBRT Field Recurrence (Tables 2 and 3, Figure 1)

Local recurrence was measured by local tumor progression within the SBRT field diagnosed on follow up CT scan. The median follow up for patients with local recurrence was 10.6 months (1.7-19.7 months) (Table 2). There were five lesions (13.5%) in five different patients that had local recurrence (Figure 1). The median time to recurrence was 10 months (2.6-13.1 months). The primary tumor location for patients with local recurrence was colorectal (40%), anal (20%), melanoma (20%) and ovarian (20%). This distribution was similar to the entire study population for colorectal and ovarian cancer (40% colorectal, 12% ovarian, 9% melanoma, and 3% anal carcinoma).

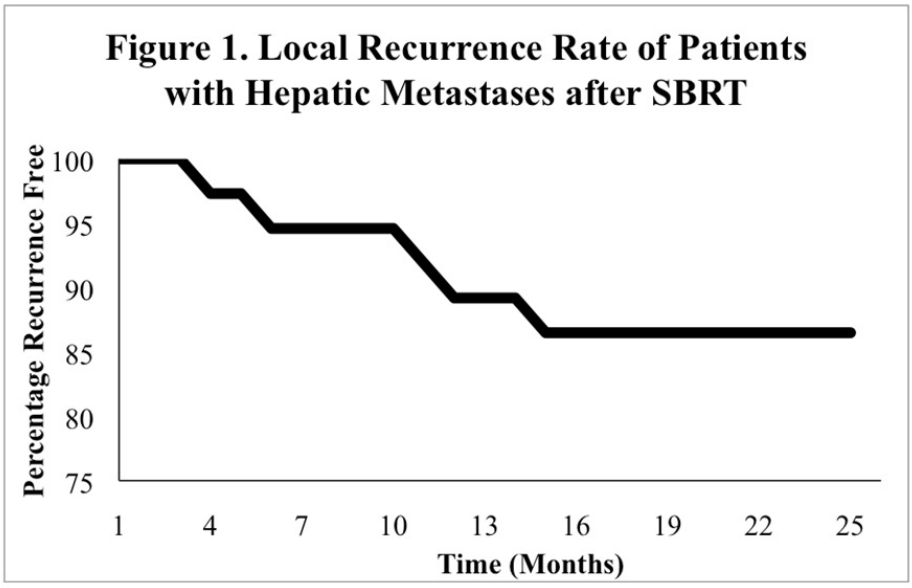
There was not a significant difference among patients with and without local recurrence when comparing median tumor size (4cm vs 4cm, 1.5 -13.9cm, p=0.216), pre-SBRT chemotherapy, primary surgical resection, or radiation. Many of the hepatic metastases were of larger size. Of the 5 local recurrences, three (60%) were in lesions less than 5cm in diameter (out of 23 lesions less than 5cm

overall) and therefore two local recurrences were in hepatic metastases greater than 5cm (out of 14 lesions greater than 5cm overall). There were 12 patients (36.4%) with metastases greater than 5cm in diameter that did not have local recurrence after SBRT, therefore the local recurrence rate for patients with metastases greater than 5cm was 14.3% (2 of 14 tumors). There were two patients with a tumor diameter greater than 10cm (11.5cm and 13.9cm), one had local recurrence after SBRT and one did not.

Table 3 Recurrence and Mortality in Patients with and without Cancer Progression

	Follow Up Post-SBRT
Follow Up Length (months)	8.1 (1.2-23.5)*
Local Recurrence within SBRT Field (n=37)	5 (13.5%)
Liver Out of SBRT Field Progression (n=33)	17 (51.5%)
Systemic Metastases (n=33)	10 (30.3%)
Any Recurrence (n=33)	25 (75.8%)
No Recurrence (n=33)	8 (24.2%)
Mortality (n=33)	18 (54.5%)
*Median (Range)	

There was no significant difference in local recurrence rates based on number of fractions (p=0.362), radiation dose (p=0.534), or BED as compared to patients without any type of recurrence. The median dose for patients with local recurrence was 28.5 Gy with a BED of 46.3 Gy while the median dose for patients without recurrence was 30 Gy (25-36Gy) with BED of 50 Gy. Three patients (60%) who had local recurrence were treated with less than 30 Gy and radiobiological equivalent dose less than 50 Gy. Recurrence rate based on BED was 21.4% (3 of 14) for BED less than 50 and 8.7% (2 of 23) for BED greater than 50 Gy.



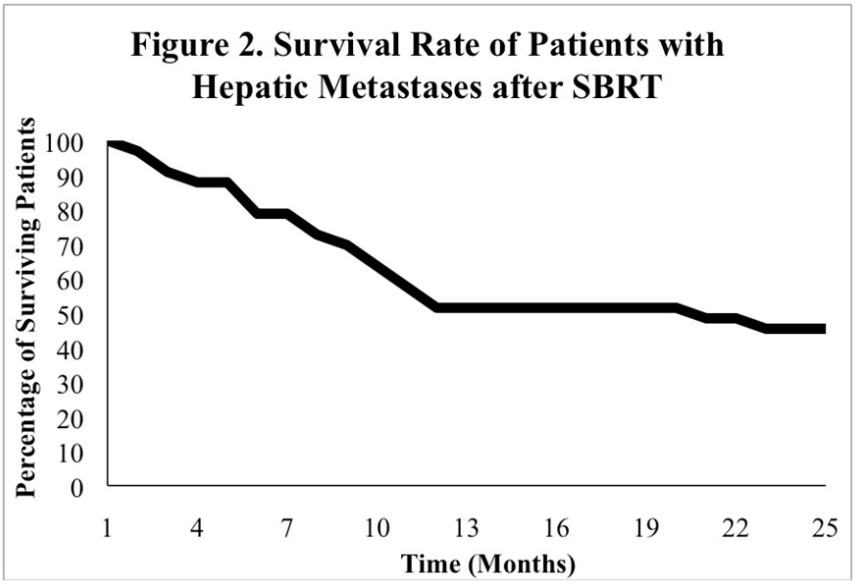
Liver Out-Of SBRT Field Progression and New Systemic Metastases (Table 3)

Seventeen patients (51.5%) progressed regionally within the liver, out of the SBRT field (Table 3). This was diagnosed on follow up CT scans as increased tumor volume outside of the SBRT field within the liver. The median follow up for patients who experienced out of field progression after SBRT was 7.4 months (1.4-20.1 months). There was a median time period from SBRT to recurrence of 5.1 months (0.8-17.5 months).

Ten patients (30.3%) had systemic recurrence in the following locations: lung (4), sternum (2), spine (1), brain (1), biliary system (1), and peritoneal implants (1). The median follow up period for patients who had systemic metastases after receiving SBRT was 10.6 months (6.5-21.1 months). Patients with systemic recurrence had a median time period from SBRT to recurrence of 5.1 months (2.2-15.6 months). Both populations of patients who had out of field recurrence and systemic recurrence had similar pre-SBRT primary surgical resections, chemotherapy, and radiation rates. Additionally both had similar median radiation doses, fraction doses, and number of fractions.

Survival after SBRT for Hepatic Metastases (Table 3, Figure 2)

The Kaplan-Meier survival curve of patients after SBRT is reported in Figure 2. The overall survival rate was 45.5% (15 of 33 patients) at 23.5 months with a median survival of 10.6 months. Univariate analysis demonstrated an increase in mortality in patients who had local recurrence within the SBRT field, regional out-of-field progression, and systemic recurrence (40%, 58.8% and 80%). As would be expected, there was a mortality difference, although statistically not significant, between patients with any recurrence (60%) versus patients without recurrence (25%).



Toxicities Secondary to SBRT for Hepatic Metastases (Table 4)

There were no grade 4 or 5 adverse events secondary to SBRT. Complications and toxicities secondary to SBRT are reported in Table 4. The most common complaint after SBRT was pain in 7 patients (21.2%)

followed by nausea without emesis in 5 patients (15.2%). There were not any patients that reported diarrhea or gastrointestinal distress. There was one patient who experienced an asymptomatic elevation of her liver laboratories. Wilcoxon Rank Sum Test did not reveal significant changes in total bilirubin (p=0.687), alkaline phosphatase (p=0.151), or albumin (p=0.716) before and after SBRT. There were not any patients that experienced liver failure.

Table 4 Complications and Side Effects Post SBRT (n=33)

	Short Term Follow Up Post-SBRT
Follow Up (Months)	8.1 (1.2-23.5) *
Nausea	5 (15.2%)
Diarrhea	0 (0%)
Pain	7 (21.2%)
Elevated Liver Laboratories	1 (3.0%)
Liver Failure	0 (0%)
*Median (Range)	

Discussion

While surgical resection of liver metastases remains standard treatment and may provide clinical benefits and prolonged survival [3, 4], most patients with metastatic cancer to the liver are not candidates for resection [12]. Non-resectional ablative therapies including cryotherapy, microwave ablation, and radiofrequency ablation, may provide better local control in patients not amenable to surgical resection [13]. Although these ablative therapies may impact the natural history of the disease with potentially less morbidity [13], they are limited by the size and location of the hepatic metastasis [22-26]. Ablative therapies can be offered through percutaneous and minimally invasive approaches, however not all metastases are accessible through these techniques. As chemotherapeutic and targeted agents improve, there may be an increasing population of patients who may benefit from liver directed therapy. SBRT allows for the delivery of high radiation doses to liver metastases while limiting the toxicity to the normal liver parenchyma found with standard EBRT techniques.

Chang et al retrospectively reviewed 65 patients with colorectal cancer with 102 hepatic metastases who were treated with SBRT at a median dose of 42 Gy (22-60 Gy) [40]. They found a 29% in field recurrence rate and a 45% overall survival rate after a 24 month period. These patients tolerated SBRT well without any grade 4 or 5 complications [40]. Scorsetti et al published a phase II study of 61 patients and 76 lesions treated with a median dose of 75 Gy in three fractions (BED 218 Gy). They had an in-field recurrence rate of 5.3% (4 lesions) and only one grade 3 toxicity (chest wall pain) [41].

Similar to other studies, we found that SBRT can be delivered safely to patients with hepatic metastases [40-42]. SBRT was well tolerated by the patients with few clinical complications, without any statistically significant change in hepatic laboratory values, and without any grade 4 or 5 toxicities. In this case series, there were no cases of liver failure despite a median dosage of 30 Gy of radiation. While 21.2% experienced pain and 15.2% experienced nausea secondary to SBRT, all patients returned to receive radiation over multiple fractions and completed their treatments.

Local recurrence after SBRT only occurred in five patients (13.5%). While this rate of local recurrence

is higher than some rates reported for radiofrequency and microwave ablative therapies [43, 44], this patient population included patients with larger tumors for which standard ablative therapies have higher recurrence rates and some patients who were not candidates for ablative therapy due to lesion location. It is also of interest we found similar local recurrence rates (14.3%) in larger lesions greater than 5cm. These patients with larger lesions are not ideal candidates for other liver directed therapies.

Combining our results with those of others, there is a clear trend that higher SBRT doses result in improved local control [40-42]. Although not statistically significant secondary to the small patient population, we found higher local control with a BED higher than 50 Gy. It is unclear what the ideal dose should be or where the local control curve plateaus. Our current practice is to use a BED of at least 80 Gy (five fractions of 10 Gy) and our preference is 60 Gy in three fractions (BED 150 Gy).

Our study population included many patients with advanced disease. In this study, 45.5% of patients had extra-hepatic disease prior to SBRT. These patients were likely preselected by their clinicians for SBRT because the extent of their liver metastases would have a significant impact in the morbidity and natural history of their disease. Despite the advanced disease in this heavily pre-treated population, the one year overall survival of this patient population was 45.5%.

While the limited hepatic toxicity and side effects are encouraging, there are study limitations. This is a case series examined retrospectively from a single institution with potential weaknesses inherent in this design. Larger patient numbers and a longer follow-up period in a prospective study are required to better assess the safety of this therapy. Additionally, this study included patients with different types of primary cancers and SBRT may have different radio-sensitivities depending on the primary tumor.

Conclusion

SBRT is safe and well tolerated in patients with hepatic metastases. SBRT offers a potential local therapy to patients with metastatic disease in the liver with minimal toxicities. The non-invasive nature of SBRT and the ability to treat lesions of various sizes and locations has significant appeal to patients and practitioners. This therapy may fill a role for patients with lesions not amenable to traditional ablative and surgical techniques or regional treatment in patients with extra-hepatic disease.

References

1. Robertson D, Stukel T, Gottlieb D, Sutherland J, Fisher E. Survival After Hepatic Resection of Colorectal Cancer Metastases. ***Cancer***. 2009, 115:752-759
2. Taylor I. Liver Metastases from Colorectal Cancer: Lessons from Past and Present Clinical Studies. ***Br J Surg***. 1996, 83:456-460
3. Blumgart LH, Fong Y. Surgical Options in the Treatment of Hepatic Metastasis from Colorectal Cancer. ***Curr Probl Surg***. 1995, 32:333-421
4. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic Metastases from Colorectal Carcinoma: Impact of Surgical Resection on the Natural History. ***Br J Surg***. 1990, 77:1241-1246
5. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical Resection of Hepatic Metastases from Colorectal Cancer: A Systematic Review of Published Studies. ***Br J Cancer***. 2006, 94:982-999
6. Ehrl D, Rothaug K, Hempel D, Rau HG. Importance of Liver Resection in Case of Hepatic Breast Cancer Metastases. ***Hepatogastroenterology***. 2013, 10

7. Caralt M, Bilbao I, Cortes J, Escartin A, Lazaro JL, Dopazo C, Olsina JJ, Balsells J, Charco R. Hepatic Resection for Liver Metastases as Part of the "Oncosurgical" Treatment of Metastatic Breast Cancer. ***Annals of Surgical Oncology***. 2008, 15:2804-2810
8. Niu GC, Shen CM, Cui W, Li Q. Hepatic Resection is Safe for Metachronous Hepatic Metastases from Ovarian Cancer. ***Cancer Biol Med***. 2012, 9:182-187
9. Bosquet JG, Merideth MA, Podratz KC, Nagorney DM. Hepatic Resection for Metachronous Metastases from Ovarian Carcinoma. ***HPB***. 2006, 8:93-96
10. Adam R. Chemotherapy and Surgery: New Perspectives on the Treatment of Unresectable Liver Metastases. ***Annals of Oncology***. 2003, 14:13-16
11. Pawlik T, Schulick R, Choti M. Expanding Criteria for Resectability of Colorectal Liver Metastases. ***Oncologist***. 2008, 13:51-64
12. McLoughlin JM, Jensen EH, Malafa M. Resection of Colorectal Liver Metastases: Current Perspectives. ***Cancer Control***. 2006, 13:32-41
13. Pathak S, Jones R, Tang JMF, Parmar C, Fenwick S, Malik H, Poston G. Ablative Therapies for Colorectal Liver Metastases: A Systematic Review. ***Colorectal Disease***. 2011, 13:252-265
14. Seifert JK, Morris DL. Prognostic Factors after Cryotherapy for Hepatic Metastases from Colorectal Cancer. ***Ann Surg***. 1998, 228:201-208
15. Niu R, Yan TD, Zhu JC, Black D, Chu F, Morris DL. Recurrence and Survival Outcomes after Hepatic Resection with or without Cryotherapy for Liver Metastases from Colorectal Carcinoma. ***Ann Surg Oncol.*** 2007, 14:2078-2087
16. Yan TD, Padang R, Morris DL. Long Term Results and Prognostic Indicators After Cryotherapy and Hepatic Arterial Chemotherapy with or without Resection for Colorectal Liver Metastases in 224 Patients: Long Term Survival Can be Achieved in Patients with Multiple Bilateral Liver Metastases. ***J Am Coll Surg***. 2006, 202:100-111
17. Shibata T, Niinobu T, Ogata N, Takami M. Microwave Coagulation Therapy for Multiple Hepatic Metastases from Colorectal Carcinoma. ***Cancer***. 2000, 89:276-284
18. Tanaka K, Shimada H, Nagano Y, Endo I, Sekido H, Togo S. Outcome after Hepatic Resection versus Combined Resection and Microwave Ablation for Multiple Bilobar Colorectal Metastases to the Liver. ***Surgery***. 2006, 139:263-273
19. Gillams AR, Lees WR. Radiofrequency Ablation of Colorectal Liver Metastases. ***Abdom Imaging***. 2005, 30:419-426
20. Siperstein AE, Berber E, Ballem N, Parikh RT. Survival After Radiofrequency Ablation of Colorectal Liver Metastases: 10-Year Experience. ***Ann Surg***. 2007, 246:559-565
21. Veltri A, Sacchetto P, Tosetti I, Pagano E, Fava C, Gandini G. Radiofrequency Ablation of Colorectal Liver Metastases: Small Size Favorably Predicts Technique Effectiveness and Survival. ***Cardiovasc Intervent Radiol***. 2008, 31:948-956
22. Poon RT, Ng KK, Lam CM, Ai V, Yuen J, Fan ST, Wong J. Learning Curve for Radiofrequency Ablation of Liver Tumors. ***Ann Surg***. 2004, 239:441-449
23. Curley SA, Izzo F, Delrio P, Ellis L, Granchi J, Vallone P, Fiore F, Pignata S, Daniele B, Cremona F. Radiofrequency Ablation of Unresectable Primary and Metastatic Hepatic Malignancies. ***Ann Surg***. 1999, 230:1
24. Yamakado K, Nakatsuka A, Ohmori S, Shiraki K, Nakano T, Ikoma J, Adachi Y, Takeda K. Radiofrequency Ablation Combined with Chemoembolization in Hepatocellular Carcinoma: Treatment Response Based on Tumor Size and Morphology. ***J Vasc Interv Radiol***. 2002, 13:1225-1232

25. Kuvshinoff BW, Ota DM. Radiofrequency Ablation of Liver Tumors: Influence of Technique and Tumor Size. ***Surgery***. 2002, 132(4):605-611
26. de Baere T, Elias D, Dromain C, Din MG, Kuoch V, Ducreux M, Boige V, Lassau N, Marteau V, Lasser P, Roche A. Radiofrequency Ablation of 100 Hepatic Metastases with a Mean Follow-Up of More than 1 Year. ***AJR Am J Roentgenol***. 2000, 175(6):1619-1625
27. Robertson J, Lawrence T, Walker S, Kessler M, Andrew J, Ensminger W. The Treatment of Colorectal Liver Metastases with Conformal Radiation Therapy and Regional Chemotherapy. ***Int J Radiat Oncol Biol Phys***. 1995, 32:445-450
28. Ben-Josef E, Normolle D, Ensminger WD, Walker S, Tatro D, Ten Haken RK, Knol J, Dawson LA, Pan C, Lawrence TS. Phase II Trial of High-Dose Conformal Radiation Therapy with Concurrent Hepatic Artery Floxuridine for Unresectable Intrahepatic Malignancies. ***J Clin Oncol***. 2005, 23(34):8739-8747
29. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of Radiation-Induced Liver Disease Using the Lyman NTCP Model. ***Int J Radiat Oncol Biol Phys***. 2002, 53:810-821
30. Dawson LA, Ten Haken RK. Partial Volume Tolerance of the Liver to Radiation. ***Semin Radiat Oncol***. 2005, 15:279-283
31. Ten Haken RK, Lawrence TS, McShan DL, Tesser RJ, Fraass BA, Lichter AS. Technical Considerations in the Use of 3-D Beam Arrangements in the Abdomen. ***Radiotherapy and Oncology***. 1991, 22:19-28
32. Cheng JCH, Wu JK, Huang CM, Liu HS, Huang DY, Cheng SH, Tsai SY, Jian JJM, Lin YM, Cheng TI, Horng CF, Huang AT. Radiation-Induced Liver Disease After Three-Dimensional Conformal Radiotherapy for Patients with Hepatocellular Carcinoma: Dosimetric Analysis and Implication. ***Int J Radiat Oncol Biol Phys***. 2002, 54:156-162
33. Lawrence TS, Ten Haken RK, Kessler ML, Robertson JM, Lyman JT, Lavigne ML, Brown MB, DuRoss DJ, Andrews JC, Ensminger WD, Lichter AS. The Use of 3-D Dose Volume Analysis to Predict Radiation Hepatitis. ***Int J Radiat Oncol Biol Phys***. 1992, 23:781-788
34. Wurm RE, Gum F, Erbel S, Schlenger L, Scheffler D, Agaolglu D, Schild R, Gebauer B, Rogalla P, Plotkin M, Ocran K, Budach V. Image Guided respiratory Gate Hypofractionated Stereotactic Body Radiation Therapy (H-SBRT) for Liver and Lung Tumors: Initial Experience. ***Acta Oncol***. 2006, 45:881-889
35. Schefter TE, Kavanagh BD, Timmerman RD, Cardenes HR, Baron A, Gaspar LE. A Phase I Trial of Stereotactic Body Radiation Therapy. ***Int J Radiat Oncol Biol Phys***. 2005, 62:1371-1378
36. Mendez-Romero A, Wunderink W, Van Os RM, Nowak PJ, Heijmen BJ, Nuyttens JJ, Brandwijk RP, Verhoef C, Ijzermans JN, Levendag PC. Quality of Life After Stereotactic Body Radiation Therapy for Primary and Metastatic Liver Tumors. ***Int J Radiat Oncol Biol Phys***. 2008, 70:1447-1452
37. Katz A, Carey-Sampson M, Muhs A, Milano MT, Schell MC, Okunieff P. Hypofractionated Stereotactic Body Radiation Therapy (SBRT) for Limited Hepatic Metastases. ***Int J Radiat Oncol Biol Phys***. 2007, 67:793-798
38. Herfarth KK, Debus J, Lohr F, Bahner ML, Rhein B, Fritz P, Hoss A, Schlegel W, Wannenmacher MF. Stereotactic Single-Dose Radiation Therapy of Liver Tumors: A Phase I/II Trial. ***J Clin Oncol***. 2001, 19:164-170
39. Ozhasoglu C, Saw CB, Chen H, Burton S, Komanduri K, Yue NJ, Hug SM, Heron DE. Synchrony-Cybefknife Respiratory Compensation Technology. ***Med Dosim***. 2008, 33:117-123
40. Chang DT, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, Dinniwell R, Brierley J, Kavanagh BD, Dawson LA, Schefter TE. Stereotactic Body Radiotherapy for Colorectal Liver Metastases. ***Cancer***. 2011, 117:4060-4069

41. Scorsetti M, Arcangeli S, Tozzi A, Comito T, Alongi F, Navarria P, Mancosu P, Reggiori G, Fogliata A, Torzilli G, Tomatis S, Cozzi L. Is Stereotactic Body Radiation Therapy an Attractive Option for Unresectable Liver Metastases? A preliminary Report from a Phase 2 Trial. ***Int J Radiat Oncol Biol Phys***. 2013, 86:336-342
42. Kress MAS, Collins BT, Collins SP, Dritschilo A, Gagnon G, Unger K. Stereotactic Body Radiation Therapy for Liver Metastases from Colorectal Cancer: Analysis of Safety, Feasibility, and Early Outcomes. ***Frontiers in Oncology***. 2012, 2:1-7
43. Howard JH, Tzeng CW, Smith JK, Eckhoff DE, Bynon JS, Wang T, Arnoletti JP, Heslin MJ. Radiofrequency Ablation for Unresectable Tumors of the Liver. Am Surg. 2008, 74:594-600
44. Berber E, Siperstein A. Local Recurrence after Laparoscopic Radiofrequency Ablation of Liver Tumors: An Analysis of 1032 Tumors. ***Ann Surg Oncol***. 2008, 15:2757-2764