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Review

Improved Radiotherapy for Primary and Secondary Liver Cancer: Stereotactic Body Radiation Therapy

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Abstract. *Background: Radiation therapy for primary and secondary liver cancer has been limited due to dose-limiting radiation-associated liver injury. Stereotactic body radiation therapy (SBRT) permits higher dose to tumors while minimizing radiation to uninvolved liver. The purpose of this study was to assess the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms. Materials and Methods: We performed a systematic review of prospective clinical trials published in English. Results: Fifteen studies involving 158 patients with primary tumors and 341 patients with metastases to the liver were included. Treatment was performed in 1-10 fractions to total doses of 18-60 Gy. One year local control and overall survival rates were 50-100% and 33-100% respectively. There were 13 cases of radiation-induced liver disease and 4 grade 5, 6 grade 4, and 69 grade 3 adverse events reported. Conclusion: For patients who are unable or unwilling to undergo local therapy, SBRT is safe and efficacious for treating primary and secondary liver cancer.*

Hepatocellular carcinoma (HCC) accounts for 70-85% of primary liver cancer cases and is associated with viral hepatitis, cirrhosis, and poor hepatic function (1). The incidence of primary liver cancer is increasing in developed countries due to hepatitis C and obesity, while decreasing in developing countries with the availability of the hepatitis B vaccine (2). Despite the high incidence of primary liver cancer, metastases to the liver are even more common (3). After lymph nodes, the liver is the most common site of metastasis for gastrointestinal malignancies (4) and is one of the most common sites for any type of cancer (5).

Radiation has not been used for local therapy in the treatment of primary and secondary hepatic tumors due to the risk of radiation-induced liver disease (RILD), limiting conventional radiotherapy to relatively low doses. Classic RILD is characterized by anicteric hepatomegaly, ascites, and elevated alkaline phosphatase that usually occurs two weeks to three months after radiation (6). Non-classic RILD is characterized by elevated liver transaminases (at least 5 times the upper limit of normal or at least 20 times the upper limit of normal in patients with baseline values greater than 5 times the upper limit of normal at baseline) or decline in liver function (Child-Turcotte-Pugh (CTP) score worsening by at least 2) without classic RILD that usually occurs one week to three months after therapy (7). Treatment of RILD is generally supportive with disease in a significant proportion of patients progressing to hepatic failure and death.

Mean hepatic dose is the most significant predictor of RILD with higher dose tolerated to a low effective volume (7). Normal liver tolerance with a risk of RILD less than or equal to 5% is approximately 28-30 Gy for whole liver irradiation (7). Patients with primary hepatobiliary malignancies and hepatic cirrhosis not only have worse hepatic function at baseline, but are also at increased risk of RILD compared to those with liver metastases (8).

Currently, treatment options for HCC include: potentially curative therapy (surgical resection, transplantation, and percutaneous ablation), non-curative therapy with survival benefit (chemoembolization and sorafenib), and antitumor therapy with unproven survival benefit (arterial embolization without chemotherapy, radioembolization, and systemic chemotherapy) (8, 9). However, with new radiation techniques, such as stereotactic body radiation therapy (SBRT), both primary and secondary liver cancer may be treated with radiation. SBRT for hepatic lesions, based on principles of stereotactic radiosurgery for brain lesions, was

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first described at Karolinska University Hospital (10-12). With SBRT, extracranial sites are treated with precise, high-dose, hypofractionated external radiation therapy. The goal is to deliver ablative doses to the tumor while minimizing normal tissue exposure.

The objective of this systematic review was to assess the efficacy and safety of SBRT in the treatment of primary and secondary liver cancer.

Materials and Methods

Prospective clinical trials studying outcomes after SBRT to liver lesions for patients with primary or secondary hepatic neoplasms were included. Reviewed reports were restricted to those published in English. SBRT was arbitrarily limited to 10 fractions or less. Studies focusing on treatment planning or delivery without patient outcomes were excluded. Relevant clinical outcomes included overall survival, local control, RILD, and grade 3-5 treatment-related adverse-events.

A Pubmed/MEDLINE search was last performed on October 5, 2011. The following search terms were used: liver neoplasms, liver cancer, hepatic neoplasms, hepatic cancer, liver metastasis, hepatic metastasis, neoplasm metastasis, hepatocellular carcinoma, intrahepatic cholangiocarcinoma, radiosurgery, stereotactic body radiation therapy, stereotactic body radiotherapy, and stereotactic radiotherapy. Potential studies were screened by title and abstract. The full text of potentially relevant reports were obtained and examined to determine if the reports met eligibility for inclusion. The reference lists of included studies were screened for additional reports.

Data on characteristics of trial participants, study design, trial inclusion and exclusion criteria, parameters for interventions (including fractionation, dose, and constraints), study quality, deviations from protocol, and endpoints (including overall survival, local control, treatment-related grade 3-5 adverse events, and RILD) were collected.

Results

The search of PubMed/MEDLINE provided a total of 265 citations. Of these, 219 studies did not meet the criteria for inclusion after reviewing the abstracts (*i.e.* not primary or secondary hepatic cancer, not stereotactic body radiation therapy, not a prospective clinical trial, or no relevant clinical outcomes). The full text of the remaining 46 citations was examined in greater detail. A total of 31 studies did not meet the inclusion criteria; 15 studies met the inclusion criteria and were included in this systematic review.

Table I summarizes characteristics of the included studies. The studies included 158 patients with at least 180 primary tumors (hepatocellular carcinoma or intrahepatic cholangiocarcinoma) and 341 patients with at least 430 metastases to the liver. Patients had a median age of 62 years (range 15-92 years), Karnofsky Performance Status (KPS) ≥60 or Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO)/Zubrod score ≤2, and CTP class B liver disease or better. Most had prior systemic or local therapy to the hepatic lesions and were technically or medically inoperable or declined surgery. Generally patients had no prior radiation therapy to the upper abdomen, but some were retreated with SBRT to recurrent or additional hepatic tumors. Adverse event grading was carried out most commonly according to the Common Terminology Criteria for Adverse Events (CTCAE) versions 3.0 to 4.0; but also the Common Toxicity Criteria (CTC) version 2.0; the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme; and the late effects of normal tissue-subjective, objective, management, and analytic scale (LENT-SOMA).

The results of the included studies are summarized in Table II. SBRT treatment was performed to total doses of 18-60 Gy in 1-10 fractions with single fraction doses from 4-30 Gy. One-year local control and overall survival rates were 50-100% and 33-100%, respectively. There were eight cases of classic RILD and five cases of non-classic RILD associated with progressive hepatic dysfunction reported. In addition, there were 4 grade 5, 6 grade 4, and 69 grade 3 adverse events reported. When eliminating adverse events that were not treatment-related or that occurred as a result of progressive disease, there were 3 grade 5, 4 grade 4, and 66 grade 3 adverse events. Patients with baseline hepatic dysfunction were at increased risk for worsening dysfunction.

Primary and secondary liver cancer. In a phase I/II study at the University of Heidelberg with 60 tumors (four primary and 56 metastases) in 37 patients, Herfarth *et al*. used single-dose SBRT from 14-26 Gy without toxicity greater than grade 2 (13-15). The 18-month local control rate was 68% for all patients and 81% for patients treated at 20-26 Gy, suggesting that there may be better local control with higher doses.

Low-dose (3×10 Gy) and high-dose (3×12-12.5 or 1×26 Gy) SBRT regimens were compared at the University of Wuezburg (16-17). Wulf *et al*. reported no local failures in the five patients with primary liver cancer (four HCC and one intrahepatic cholangiocarcinoma (IHC)); one patient was alive at 48 months and another alive at 17 months, three others died of multifocal tumor progression. For the 51 hepatic metastases in 39 patients, overall survival was 72% at 12 months, 32% at 24 months, and 22% at 36 months. The low-dose group had 12- and 24-month local control rates of 86% and 58%, respectively, while the corresponding rates for the high-dose group were 100% and 82% (p=0.077).

Méndez Romero *et al*. treated patients with HCC or metastases with 3×12.5 Gy except for HCC patients with tumor ≥4 cm in the setting of cirrhosis who were treated with 3×10 or 5×5 Gy (18). Their one- and two-year local control rates at were 94% and 82%, respectively. These rates were slightly better than Wulf *et al*., likely due to higher doses on average. However, the higher average doses also increased

Table I. *Characteristics of included studies*.

Author, year (reference)	Primary tumors		Metastases		Median age (years) (range)		Gender (M:F)	Median target size‡ (ml) (range)		Median follow-up (months) (range)	
	Patients	Tumors	Patients	Tumors							
Herfarth *et al*., 2004 (15)	4	4	33	56	61	(37-84)	25:12	10†	(1-132)	15.1†	(max 50.6)
Méndez Romero *et al*., 2006 (18)	8	11	17	34	63	(37-81)	20:5	22.2	(1.1-322)	12.9	(0.5-31)
Wulf *et al*., 2006 (17)	5	5			68	(52-78)	3:2	114C	(14-516)	15	(2-48)
			39	51	60	(15-80)	21:30	53C	(9-355)	15	(2-85)
Tse *et al*., 2008 (23)	41	NR			62	(41-85)	41:10	173	(9-1913)	17.6	(10.8-39)
Ambrosino *et al*., 2009 (32)			27	NR	62†	(47-80)	NR	69	(20-165)	13	(6-16)
Lee *et al*., 2009 (27)			68	NR	63†	(30-90)	32:36	75.2	(1.2-3090)	10.8	NR
Rusthoven *et al*., 2009 (30)			47	63	58	(27-92)	NR	14.9	(0.75-98)	16	(6-54)
Cárdenes *et al*., 2010 (24)	17	25			61	(46-83)	16:1	34	(8-95)	24	(10-42)
Goodman *et al*., 2010 (20)	7	NR	19	NR	63	(23-84)	14:12	32.6	(0.8-147)	17.3	(2-55)
Iwata *et al*., 2010 (21)	6	NR	12	NR	72	(54-84)	10:8	42.4P	(19-101)	14.5	(4-21.5)
Shin *et al*., 2010 (26)	6	6			48	(44-55)	NR	1288	(1008-1815)	25.9	(8.1-56)
Stintzing *et al*., 2010 (19)			36	54	65	(33-87)	18:18	17.9	(2.2-90)	21.3	(2.8-44)
van der Pool *et al*., 2010* (31)			20	31	72	(45-81)	15:5	2.3 cm	(0.7-6.2 cm)	26	(6-57)
Andolino *et al*., 2011 (25)	60	71			59	(24-85)	49:11	29	(2-112)	27	NR
Rule *et al*., 2011 (33)			27	37	62	(48-86)	17:11	9.5I	(0.75-135)	20	(4-53)

*Population may overlap with that of (18); †mean; NR, not reported; ‡gross tumor volume unless otherwise indicated; C, clinical target volume; I, internal target volume; P, planning target volume.

toxicity. Two patients with CTP-B developed RILD (one classic and one non-classic) and two patients treated for metastases developed non classic RILD.

Stintzing *et al*. applied the single-fraction SBRT of Herfarth *et al*. to a dose of 24 Gy to 36 patients with 54 tumors (19). They report no significant treatment-related toxicity with better one-year local control (95%) and overall survival (83%). To assess the safety of single-fraction SBRT in patients with chronic liver disease, Goodman *et al*. treated 26 patients with CTP-A liver disease with 18-30 Gy (20). There was no grade 3 or higher toxicity or RILD. Median survival was 28.6 months, two-year overall survival was 50.4%, and the risk of local failure at one year was 23%. Overall survival at one year and two years for patients with primary liver tumors was 71.4% and 53.6%, respectively, and for those with metastatic disease was 61.8% and 49.4%, respectively.

At the other end of the SBRT spectrum, Iwata *et al*. employed 10-fraction SBRT to total dose of 50-55 Gy for 17 patients with CTP-A and 1 patient with CTP-B liver disease (21). They reported one-year local control of 86% and one-year overall survival of 94% without RILD or significant toxicity.

Primary liver cancer. Patients with primary liver cancer tend to have worse hepatic function, which increases the risk of radiation-associated liver injury, so trials with primary liver cancer patients with CTP class A and B chronic liver disease have been performed. In a phase I trial of 31 patients with CTP-A HCC and 10 patients with IHC, Dawson *et al*. found a median survival of 13.4 months, one-year overall survival of 51% and one-year local control of 65% (22, 23). There was no dose-limiting toxicity or RILD using a 6×4-9 Gy regimen. There were no grade 4 or 5 impact on liver enzymes, but 25% had grade 3 impact on liver enzymes and disease in 23% progressed from CTP-A to CTP-B within three months.

At Indiana University, in a phase I study, Cárdenes *et al*. treated 17 HCC patients with CTP-A or CTP-B, 1-3 lesions and cumulative tumor diameter ≤6 cm (24). Patients with CTP-A were treated in three fractions with the dose escalated from 12 to 16 Gy. For patients with CTP-B, the dose was modified to five fractions starting at 8 Gy per fraction and was not escalated because two patients treated at 3×14 Gy developed grade 3 hepatic toxicity and RILD. The one-year overall survival was 75% and there were no local failures during their median 24 months of follow-up.

Building upon the phase I study, 36 patients with CTP-A disease were treated with 3×18 Gy and 24 patients with CTP-B disease were treated with 5×8 Gy (25). With this regimen, Andolino *et al*. reported complete response, partial response, and stable disease for 30%, 40%, and 25% of tumors, respectively. Two-year local control, progression-free survival, and overall survival were 90%, 48%, and 67%, respectively, with a median progression-free survival of 20.4 months and overall survival of 44.4 months.

In an attempt to extend the use of SBRT to larger lesions, Shin *et al*. treated six patients with large tumors (median tumor volume 1288 ml, range 1008-1815 ml) with no worse than CTP-A liver disease and without extrahepatic metastases (26). The 4×8–10 Gy regimen was relatively safe,

Table II. *Results of included studies*.

Author, year (reference)	Total dose (Gy) (fractions × dose/fraction)		Local control	Overall survival	Treatment-related grade 3-5 toxicity
Herfarth *et al*., 2004 (15)	14-26	(1×14-26)	1-Year 71% 1.5-Year 68% (overall) 81% (>20 Gy)	1-Year 72% Median 25 months (overall), 27 months (>20 Gy)	None
Méndez Romero *et al*., 2006 (18)	25-37.5	(3×10-12.5 or 5×5)	1-Year 94% 2-Year 82%	1-Year 82% 2-Year 54%	RILD classic (1), non-classic (3); grade 5 after grade 4 LE, portal hypertension, esophageal variceal bleeding (1); grade 3 GGT (2), weakness (1), esophageal variceal bleed (1)
Wulf *et al*., 2006 (17)	26-37.5	(3×10-12.5 or 1×26 or 4×7)	For primary 100% at last follow-up	1-Year 60% Median 15 months	None
			For metastases 1-Year 92% 2-Year 66%	1-Year 72% 2-Year 32% Median 16 months	None
Tse *et al*., 2008 (23)	24-54	(6×4-9)	1-Year 65%	1-Year 51% Median 13.4 months	Grade 3 LE (10), platelets (1); GI bleed from tumor-duodenal connection ($1^{\dagger}$) & SBO ($1^{\dagger}$); CTP Progression A-B (7/41)
Ambrosino *et al*., 2009 (32)	25-60	(3×8-20)	Crude 74%	NR	None
Lee *et al*., 2009 (27)	27.7-60	(6×4.6-10)	1-Year 71%	1.5-Year 47% Median 17.6 months	Grade 5 SBO + grade 4 duodenal bleed ($1^{\dagger}$); grade 4 SBO/abdominal hernia ($1^{\dagger}$); grade 3 gastritis/ esophagitis (2), nausea (2), platelets (1), lethargy (1), LE ($1^{\dagger}$), LE+bilirubin ($1^{\dagger}$); CTP progression A-B (3/68), A-C (1/68)
Rusthoven *et al*., 2009 (30)	36-60	(3×12-20)	1-Year 95% 2-Year 92%	2-Year 30% Median 20.5 months	Grade 3 soft tissue toxicity (1)
Cárdenes *et al*., 2010 (24)	36-48	(3×12-16 or 5×8)	100% At last follow up	1-Year 75% 2-Year 60%	RILD classic (3); grade 4 bilirubin (1); grade 3 platelets (4), LE (3), bilirubin (3), INR (1), albumin (1), leukocytes (1)
Goodman *et al*., 2010 (20)	18-30	(1×18-30)	1-Year 77%	1-Year 64.3% 2-Year 50.4% Median 28.6 months	None
Iwata *et al*., 2010 (21)	50-55	(10×5-5.5)	1-Year 86%	1-Year 94%	None
Shin *et al*., 2010 (26)	32-40	(4×8-10)	1-Year 50%	1-Year 33% Median 10 months	Grade 3 LE ($1^{\dagger}$)
Stintzing *et al*., 2010 (19)	24	(1×24)	1-Year 95%	1-Year 83% 2-Year 62% Median 25.1 months	None
van der Pool *et al*., 2010* (31)	37.5-45	(3×12.5-15)	1-Year 100% 2-Year 74%	1-Year 100% 2-Year 83% Median 34 months	Grade 3 GGT (2), weakness (1)

Table II. *Continued*

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Author, Year (reference)	Total dose (Gy) (fractions × dose/fraction)		Local control	Overall survival	Treatment-related grade 3-5 toxicity
Andolino *et al*., 2011 (25)	40-48	(3×16 or 5×8)	2-Year 90%	2-Year 67% Median 44.4 months	RILD classic (4 with 2 deaths), non-classic (2); grade 4 platelet & bilirubin (1); grade 3 platelets (9), bilirubin (7), LE (2), INR (2), albumin (7); CTP progression A-B (7/36), B-C (5/24)
Rule *et al*., 2011 (33)	30-60	(3×10 or 5×10 or 5×12)	1-Year 56% (30 Gy) 100% (50 Gy) 100% (60 Gy) 2-Year 56% (30 Gy) 89% (50 Gy) 100% (60 Gy)	2-Year 56% (30 Gy) 67% (50 Gy) 50% (60 Gy) Median 37 months	None

*Population may overlap with that of (18); †associated with disease progression; CTP, Child-Turcotte-Pugh; GGT, gamma-glutamyl transpeptidase; GI, gastrointestinal; INR, international normalized ratio; LE, liver enzymes; RILD, radiation-induced liver disease; NR, not reported; SBO, small bowel obstruction.

with only one case of grade 3 changes in transaminases. However, one-year overall survival was only 33%, in part due to advanced disease.

Secondary liver cancer. Patients with liver metastases may have different baseline characteristics, response to treatment, and complications, so studies of patients with metastases alone were carried out. Lee *et al*. performed SBRT in six fractions to total doses of 27.7-60 Gy for 68 patients with metastatic disease to the liver (27). There was local control of 71% at one year with median and 18-month overall survival of 17.6 months and 47%. They reported worsening liver dysfunction in four patients (disease in three progressed from CTP-A to CTP-B and in one from CTP-A to CTP-C).

In a multi-institutional study of 63 lesions in 47 patients with one to three hepatic metastases of maximum individual tumor diameter of 6 cm, Rusthoven *et al*. escalated the dose from 36 to 60 Gy in three fractions without dose-limiting toxicity (28-30). One- and two-year local control rates were 95% and 92%. Overall survival at two years was 30%. Median survival was 20.5 months overall, 12 months for those with unfavorable primaries (lung, ovary, and non-colorectal gastrointestinal) and 32 months for those with favorable primaries (breast, colorectal, renal, carcinoid, gastrointestinal stromal tumor, and sarcoma) ($p<0.001$). Compared to the trial of Lee *et al*., there was smaller tumor volume (15 ml *vs*. 75 ml), less extrahepatic disease (48% *vs*. 53%), and restrictions on the number of metastases (3 *vs*. up to 8).

Other three-fraction schemes also had low rates of adverse events. Van der Pool *et al*. reported two cases of grade 3 GGT elevation and one case of grade 3 weakness out of 20 patients treated in three fractions to 37.5-45 Gy (31). They had 100% local control and overall survival at one year. Ambrosino *et al*. used three fraction SBRT to total doses of 25-60 Gy without treatment-related toxicity (32).

Rule *et al*. treated 27 patients and 37 metastases with 3×10, 5×10, or 5×12 Gy (33). They found significantly different local control (at one/two years) for 60 Gy compared to 30 Gy (100%/100% *vs*. 56%/56%, $p=0.009$) but no difference between 50 Gy (100%/89%) and 30 Gy ($p=0.09$) or 60 Gy ($p=0.56$). In addition, there was no difference in overall survival between groups, with two-year overall survival of 56%, 67%, and 50% for those treated with 30, 50, and 60 Gy, respectively.

Discussion

SBRT fractionation schemes that have been most commonly reported in prospective trials for primary and secondary liver cancer use single- or three-fractions at 1×24-30 Gy or 3×15-20 Gy. Other regimens included: 5×8-10 Gy, 6×8-10 Gy, and 10×5-5.5 Gy.

In patients unable or unwilling to undergo surgical resection or other local therapy, SBRT is associated with one-year local control and overall survival rates of 50-100% and 33-100%, respectively. A few of the studies noted better local control and survival with higher doses (16, 18, 29). Poorer local control of primary liver cancer may be due to larger tumor sizes and lower radiation doses. As a comparison, long-term overall survival for patients with HCC treated with curative intent with other local therapies such as resection, radiofrequency ablation, and chemoembolization range from 50 to 70% at five years, while initial response to non-curative treatment ranges from 16 to 60% (10).

Treatment-related adverse events occurred at a crude rate of 17% (73 events for 499 patients), with 7 out of 15 studies reporting no significant toxicity. The rate of treatment-related adverse events was greater for patients with primary liver cancer: there were 2 cases of RILD and 13 grade 3 treatment-related adverse events in patients with metastases compared to 11 cases of RILD and 73 grade 3 or higher treatment-related adverse events occurred in patients with primary liver cancer. The increased risk of treatment-related toxicity is likely in part due to the fact that primary liver cancer, specifically HCC, tends to occur in patients with cirrhosis and poor hepatic function at baseline compared to patients with hepatic metastases. Various techniques have been proposed to minimize the risk of radiation-associated liver injury, including using lower total doses for patients with cirrhosis, minimizing mean dose to the liver, and sparing a critical volume of liver (7, 34).

There are a few limitations of this analysis. Although the included studies were prospective, there were no reports of randomized trials comparing SBRT to another treatment modality for liver lesions. In addition, for primary liver cancer, there are few trials with patients with CTP class B or C liver dysfunction and tumor types were limited to HCC and IHC without rarer primary liver cancer.

In conclusion, in patients who are unable or unwilling to undergo surgical resection or other local therapy, SBRT is safe and efficacious for the treatment of primary and secondary liver cancer. Further optimization of dosing and fractionation are needed. Larger, longer-term, phase III clinical trials would permit the comparison of SBRT to surgical resection, radiofrequency ablation, or transplantation.

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