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NRG Oncology/RTOG 0438: A Phase I Trial of Highly Conformal Radiation Therapy for Liver Metastases

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Abstract

Purpose: To determine the feasibility and the maximally tolerated dose (MTD) of hypofractionated, conformal radiation therapy (RT) in patients with liver metastases.

Methods: Eligibility criteria included non-surgical pts with ≤ 5 liver metastases; sum of maximal diameter of all lesions ≤ 8 cm. There were four dose levels: 35 Gy, 40 Gy (starting level), 45 Gy and 50 Gy in 10 fractions. The clinical target volume (CTV) included metastases identified on contrast CT or MRI with a 5 mm margin within the liver. The planning target volume (PTV) margin ranged from 4 to 30 mm, dependent on breathing motion. Dose limiting toxicities (DLTs) were defined as RT related grade ≥ 4 hepatic, gastrointestinal (GI) or thrombocytopenia occurring within 90 days of the start of RT.

Results: 26 patients with metastases from colorectal (8), breast (7) and other malignancies (11) were enrolled between 11/2005 and 12/2010. 23 patients were evaluable (8, 7, & 8 on the 40, 45, & 50 Gy dose levels respectively). Two patients assigned to 50 Gy received 35 Gy due to normal tissue limits, so 2 additional patients were treated to 50 Gy. There were no DLTs on any of the dose levels. On the 45 Gy dose level, 1 patient developed reversible grade 3 enteritis (37 days from RT start) and diarrhea (22 days) while another patient developed grade 3 lymphopenia (23 days). On the 50 Gy dose level, 1 patient had grade 3 hyperglycemia (74 days) and another patient developed grade 3 lymphopenia (13 days), colonic hemorrhage (325 days), and colonic GI

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obstruction (325 days). With a potential median follow-up of 66.1 months (34.6 – 89.0 months), there were no other late toxicities observed.

Conclusions: Treatment of liver metastases with 50 Gy in 10 fractions was feasible and safe in a multi-institutional setting.

INTRODUCTION

Liver metastases from many cancers are a common cause of cancer morbidity and death. Thirty to 70% of patients with cancer have been found to have liver metastasis at autopsy. In 1995, the concept of 'oligo-metastases' was introduced, referring to a state of intermediate metastases, when a patient presents with metastases in only a limited number of regions, before the development of wide spread metastases, at a time when local therapy may lead to sustained local control and improved survival (1,2). Liver metastases are often solitary or limited in number, representing 'oligo' metastases.

Resection of liver metastases from colorectal carcinoma can lead to 5-year survival rates of 40% to 60% (3, 4), and resection has also led to sustained local control and survival for liver metastases from other cancers, such as renal cell carcinoma, sarcoma, melanoma, gynecological carcinomas, and breast cancer. (5)

A subset of patients who present with liver metastases are not suitable for resection due to operative risks, medical contraindications, wide extent of metastases or high risk for diffuse occult distant metastases (6) Also, many patients develop liver confined recurrences following resection. Systemic therapy represents the standard of care for most of these patients. For patients with metastases from colorectal cancer, survival has substantially improved in the past 10 years from a median survival of 10 months with single agent fluouracil to > 24 months with combinations of irinotecan, oxaliplatin, and bevacizumab (7). These improved outcomes are also likely related to the increased use of resection or other local therapies for liver metastases (7).

Radiofrequency ablation (RFA) is an effective ablative therapy for patients with metastases less than 3 cm, away from large vessels (8). Although less invasive than surgery, RFA requires placement of electrodes into the tumor, with a small risk of bleeding, infection or less commonly tumor tracking. Furthermore, RFA is most often not suitable for treatment of metastases in the portahepatic region (8). Successful local treatment of patients with metastases in the caudate portion of the liver, especially if accomplished with low toxicity, could prolong life and reduce morbidity for many patients.

Theoretical benefits of using radiation therapy for treatment of patients with unresectable liver metastases include ablating or debulking known gross tumor, potentially increasing the effectiveness of chemotherapy and other systemic therapies. In pre-clinical models, higher doses per fraction are associated with novel mechanisms of tumor kill, including increased tumor antigenicity (9,10) and cell death via the ceramide endothelial target pathway, (11). Hypofractionated radiation therapy is also more convenient for patients than standard fractionation.

Conformal hyperfractionated radiation therapy (RT) has been shown to be safe for focal unresectable focal liver metastases (12). Stereotactic body radiation therapy (SBRT) refers the use of highly precise and accurate radiation therapy, generally to small volumes, in 1 or few fractions. SBRT (sometimes referred to as steretactic ablative radiation therapy or SABR), generally refers to delivery of highly conformal radiation therapy in 5 or fewer fractions; however, this cutoff is arbitrary, and stereotactic techniques may be used to facilitate safe hypofractionation delivered in more than 5 fractions, as was done in the present study, albeit with less advanced radiation technologies compared to those widely available today (e.g. conformal planning without IMRT was used in the present study).

NRG Oncology/RTOG 0438 was designed to identify the maximally tolerated dose of highly conformal, high dose per fraction radiation therapy delivered in 10 fractions, in patients with liver metastases. The rationale for 10 fractions was that excellent outcomes had been observed following 10 fraction conformal RT for metastases at University of Rochester (13,14).

METHODS AND MATERIALS

Patients

Patients were eligible if they had pathologically confirmed non-lymphoma liver metastases or new radiographic liver lesions consistent with metastases in a patent with histologically proven cancer. Patients could have up to 5 metastases with total sum of maximum diameter for all lesions ≤ 8 cm, on contrast-enhanced liver CT or MR imaging obtained within 6 weeks prior to study entry. Metastatic disease outside the liver was permitted if the hepatic disease was thought to be life-limiting. Previous liver resection or ablative therapy was permitted. Pretreatment laboratory studies included absolute neutrophil ≥ 1800 cells/mm^3, hemoglobin ≥ 8.0 g/dl, and platelet count > 100,000 cells/mm^3.

Exclusion criteria were: CNS metastases, liver cirrhosis, prior invasive malignancy (other than primary cancer for metastases and non-melanoma skin cancer) unless disease-free for a minimum of 3 years, or prior external beam radiation therapy to the abdomen. Patients could not have had chemotherapy within the 4 weeks prior to radiation therapy, with no planned chemotherapy in the 4 weeks after radiation therapy. Informed consent approved by the institutional review board of each participating center was obtained from all patients.

Treatment

CT based 3D treatment planning was used for all patients. IMRT was not permitted. The gross tumor volume (GTV) included all the hepatic metastases as seen on IV contrast enhanced CT and/or MR. The clinical target volume (CTV) was defined as the GTV with a 5 mm extension within the liver. A minimum of 4 mm and maximum of 30 mm was added for the planning target volume (PTV), depending on the patient tumor motion and the motion management strategy used. Note the smallest PTV that could be used based on available motion management and IGRT was recommended to be used. Approved methods for compensation of respiratory motion included abdominal compression, active breath hold

techniques, and respiratory gating. Image guided radiation therapy (IGRT) using a soft tissue surrogate for the tumor was recommended.

All centers that participated in this study completed a 3D facility questionnaire, a protocol specific 'dry run' planning case, and successfully irradiated a standardized phantom provided by the Radiological Physics Center (RPC) at MD Anderson Cancer Center. The questionnaire described the motion management strategy to be used, as well as institutional reproducibility of the technique. The dry run plan was provided by the institution (from a previous patient who would have been eligible for the study or a patient with a simulated 4 cm liver tumor), planned with 40 Gy in 10 fractions as per the study, then submitted for central review by the Image-guided Therapy Center (ITC) remote review tool. There was no real time / pretreatment radiation plan review for this study. All patient plans were submitted for central review to the ITC. There was no credentialing for or review of image guided radiation therapy (IGRT) since there was no standard acceptance criteria at the time of this study.

The prescription dose was 35, 40, 45, or 50 Gy in 10 consecutive fractions, dependent on the dose level. The prescription dose was intended to cover the PTV, and the minimum permitted dose to 99% of the PTV was 90% of the prescription dose. The maximum permitted dose within the PTV was 120% of the prescription dose. The liver volume minus the GTV (referred to as 'liver' for the rest of the manuscript) had to be at least 1000cc, and no more than 30% and 50% of the liver could receive 27 Gy and 24 Gy, in ten fractions, respectively. No more than 33% of the combined renal volume could receive 18 Gy or more, and the maximal permitted dose to 1cc of the small bowel (including the duodenum) and 1 cc of the stomach was 37 Gy.

Patient Evaluation

Patients were evaluated weekly during RT with physical examination, toxicity assessments, and laboratory studies, including complete blood counts, liver enzymes and liver function tests including albumin, INR and bilirubin. These assessments were repeated 1 month following completion of RT and then every 3 months for the first year, every 4 months for the second year, and every 6 months for the third year, at which point patients were followed as per standard of care.

Assessment for response to RT was done locally using IV contrast liver CT or MR scans obtained at every follow-up visit as per institutional guidelines, until intrahepatic progression was documented on imaging, using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (15). Extra-hepatic imaging was obtained as per standard local practice.

Dose-limiting Toxicities

Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 criteria (CTCAE v. 3.0). DLTs were defined as any of the following occurring within 90 days from the start of treatment: grade 4 or 5 hepatic/gastrointestinal/thrombocytopenia, radiation induced liver disease (RILD) requiring treatment (defined as: i grade 3 or higher alkaline phosphatase (ALP) in the

presence of ascites occurring in the absence of disease progression or ii grade 4 hepatic liver enzyme elevations persisting for ≥ 5 days), or any grade 5 treatment-related AE. In addition, any AE requiring interruption of therapy by ≥ 2 was considered a DLT, excluding patient desire to discontinue therapy.

Statistical Methods

The primary endpoint of the study was to determine the maximally tolerated dose (MTD) of highly conformal RT in patients with liver metastases, such that the rate of DLT was less than 35%. There were four dose levels, 35 Gy (level I), 40 Gy (level II), 45 Gy (level III), and 50 Gy (level IV) given in ten fractions. Patients were enrolled starting at dose level II. After 6 evaluable patients were enrolled for a given dose level, the study was temporarily closed for toxicity evaluation. All patients treated at each dose level were followed for a minimum of 90 days from the start of treatment for DLT assessment. If there was no more than one DLT per level, the study was reopened for accrual at the next dose level. Otherwise, the preceding dose level would be declared to be the MTD. If there were 2 or more DLTs at the starting dose level (dose level II), then the dose would be de-escalated to dose level I. If this occurred and there was 0 or 1 DLT, dose level I would be declared to be the MTD. With 6 evaluable patients on each dose level, the probability of not escalating when the true DLT rate is 35% or higher was at least 68%. If the true DLT rate was 20%, the probability that the dose would be escalated was 66%.

RESULTS

Patient Characteristics

Between November 3, 2005 and December 20, 2010 26 patients were enrolled and 23 patients were evaluable (dose level II-40 Gy, 8 patients; dose level III-45 Gy, 7 patients; dose level IV-50 Gy, 8 patients). Patients were treated at three institutions Princess Margaret Cancer Centre, University of Toronto, Ontario, University of Rochester Medical Center, Rochester, New York, and McGill University, Montreal, Quebec. Two of the patients assigned to Level IV received only 35 Gy (dose level I) because of normal tissue constraints, therefore 2 additional patients were accrued and treated to 50 Gy, in 10 fractions. Reasons for trial exclusion included no protocol treatment received (n=2), and chemotherapy not completed within 4 weeks prior to radiation therapy (n=1).

The majority of patients had metastases from colorectal carcinoma (n=8, 35%) and breast cancer (n=7, 30%) (Table 1). Most patients had received prior systemic therapy (n=19, 83%) and had a single metastases (n=14, 61%) (maximum of 3), with the majority of lesions measuring 1 to 3 cm (n=8, 57%).

Radiation Therapy

All patients were treated with highly conformal RT, using 6 to 18 MV. The most common types of breathing motion management were active breathing control and abdominal compression. All patients completed radiation therapy as planned with no acute toxicity leading to treatment interruption.

On central review, the majority of RT plans were per protocol (Table 2). Eighty-seven percent (20 of 23 cases) had target volume contours per protocol, and 3 had acceptable variations (due to lack of IV contrast in one). Eighty-seven percent (20 of 23 cases) had organs at risk (OAR) contoured per protocol; one OAR was an acceptable variation, while two OAR contours were unacceptable (due to no small bowel contouring). Eighty-three percent (19 of 23 cases) had target volume dosimetry as per protocol, while four cases had target doses that were unacceptably too low. Ninety-seven percent (22 of 23 cases) had OAR dosimetry as per protocol, and one case had an unacceptable variation due to too high liver dose and no small bowel doses reported, as shown in Tables 3 and 4.

Toxicities

The median (min-max) follow-up of all patients was 24.1 months (9.7 – 62.8 months), and in alive patients was 52.8 months (47.1 – 58.5 months). There were no DLTs observed. There were two (28.6%) patients on dose level III, and 2 (25.0%) patients on dose level IV with grade 3 AEs reported as definitely, probably, or possibly related to treatment. On level III, 1 patient had clinically insignificant, transient, grade 3 lymphopenia 23 days after the start of RT, and another patient developed reversible grade 3 enteritis and grade 3 diarrhea 37 and 22 days post RT start, respectively. In this patient, the maximal doses to 0.5 cc and 5 cc of small bowel were 37.8 Gy and 29.4 Gy in 10 fractions, respectively. On Level IV, one patient had grade 3 hyperglycemia 74 days post RT start, and 1 patient developed a grade 3 colonic hemorrhage and colonic obstruction (325 days post RT start), as well as transient, grade 3 lymphopenia (13 days post RT start). In this patient, the maximal doses to the colon were not recorded; the maximal point doses to 0.5cc and 5 cc of small bowel were 19.8 Gy and 12.9 Gy in 10 fractions, respectively. All treatment-related grade ≥ 3 toxicities are summarized in Table 5. rade 1 and 2 fatigue, nausea were common, and grade 1 or 2 elevation of liver enzymes was seen occasionally in patients treated on dose levels III and IVs. Grade 1 thrombocytopenia was also seen in three patients (1 on level II and 2 on level IV), and no grade ≥ 2 thrombocytopenia was observed. There was one grade 1 chest wall pain (level II), and 8 cases of grade 1 abdominal pain (3 level II, 3 level III and 2 level IV). There were no reported cases of rib fractures or biliary toxicity.

Since there were no DLTs at any dose level, the maximum tolerated dose is 50 Gy in 10 fractions. Patients were selected so that the predefined normal tissue constraints could be met. That is, the tumors treated at the higher dose levels were not directly adjacent to the stomach or bowel which would have limited the dose that could be delivered safely.

Overall survival

The median survival of all patients was 24.1 months (min-max: 9.7 – 62.8, Table 6). The primary cause of death was due to extrahepatic cancer progression. Seven (33%) patients were reported to have died of progression of liver metastases (4 on level II, 1 on level III, and 2 on level IV). Two patients, 1 from dose level III and 1 from level IV, are alive with no progressive cancer at the time of their last follow-up, at 58.5 and 47.1 months, respectively.

DISCUSSION

This phase I study of hypofractionated, highly conformal RT for unresectable liver metastases demonstrated that a dose of 50 Gy in 10 fractions was feasible and safe in a multi-institutional setting, with no dose limiting toxicities observed. Despite the biologically effective doses being far lower than SBRT doses, the median survival was high. In fact, some of the patients on this study were alive years following RT, with no tumor progression or subsequent therapies.

Lessons learned from this study include the importance of credentialing, and of defining all normal tissue dose limits up front. On central review, the majority of cases (87%) were contoured as per protocol; 3 of 23 patients had acceptable variations in target volumes, and 3 patients had variations in OAR contours (1 acceptable and 2 unacceptable). The large bowel didn't have a predefined maximal dose limit, and one patient treated on dose level IV developed grade 3 colonic toxicity. Similarly, the majority of plans were per protocol (83% and 96% for target and OAR dosimetry). The primary reason for variations was due to tumor doses being too low, and liver doses being too high. These variations are likely a reflection of competing PTV coverage and OAR dose sparing, which may occur due to tumors being adjacent to luminal gastrointestinal tissues or multiple tumors occurring in different lobes of a small liver leading to challenges in sparing the liver. Peripheral liver metastases are not uncommon, and the maximal doses that may be delivered to these metastases is often limited by adjacent stomach, small or large bowel. The patients who were treated on this study at the higher dose levels did not have tumors adjacent to luminal gastrointestinal tissue. Patients with tumors adjacent to luminal gastrointestinal tissues are often not able to be treated with ablative doses, leading to worse local control and survival, compared to patients with tumors distal from luminal gastrointestinal tissues that may be treated to higher doses. Strategies to 'move' luminal gastrointestinal tissue away from liver tumors, for example with 'spacers', are desirable for such (16).

What the most appropriate doses are for treating liver metastases is not clearly defined. Others have shown that breast cancer metastases tend to be better controlled with RT, compared to colorectal carcinoma or other metastases (14, 17, 18). One report of stereotactic body radiation therapy (SBRT) for colorectal carcinoma liver metastases found that the dose associated with a 90% chance of local control was 46 – 48 Gy in 3 fractions (19), far higher biologic doses than what was delivered in this study. Such hypofractionated doses cannot be safely delivered to metastases directly adjacent to luminal gastrointestinal cancers (20), and may increase the risk of biliary toxicity (21, 22).

Since the time that this study was conducted, there have been a rapidly increasing number of reports on SBRT for unresectable liver metastases and other oligo-metastases (23–29). In general, higher doses have been associated with improved local control, at least for colorectal carcinoma and most other non-breast cancer metastases. Toxicities reported unique to SBRT include chest wall pain or rib fractures, often requiring treatment. This was not seen in the present study of conformal RT delivered in 10 fractions, although transient grade 1 chest wall pain was seen in 1 patient. The absence of biliary toxicity in the present study is also notable, as late biliary toxicity is becoming recognized as a potential late

toxicity following SBRT (21, 22). Although one would expect a lower risk of biliary toxicity with 10-fraction conformal radiation therapy compared to SBRT, doses to the central biliary structures were not recorded, so it is not possible to know with certainty what the exact risk of biliary toxicity is in 10 fractions, although it is hypothesized that the risk is low for doses less than 50 Gy in 10 fractions. Of note, in the present study, DLT was not seen at the 50 Gy in 10 fraction dose level, and higher doses may be possible to be delivered safely, especially if smaller PTVs with more advanced stereotactic planning and IGRT techniques are used.

Although there are many SBRT series published (22–30), few have long follow-up. In the present series, despite using lower biologic doses, a minority of patients are alive years following RT without long term toxicities. The most suitable patients with oligometastases for RT remains unclear, and future research efforts are needed to help in more appropriate selection of patients. Recently, randomized phase II trials have demonstrated that SBRT improves progression-free survival for non-small cell lung cancer oligo-metastases (< 3 sites) compared to systemic therapy alone (29, 30). Palma et al also completed a randomized phase II trial of SBRT for oligo-metastases from a variety of primary tumors (SABR-COMET trial) (31). Ninety-nice patients, generally with 1 to 3 metastases, mostly from breast cancer, were randomized 2:1 to SBRT of standard of care. SBRT was associated with a statistically significant improvement in progression free survival from 6 months to 12 months (p=0.001), and a trend for improved survival (median overall survival 41 months versus 28 months, for SBRT versus no SBRT, p=0.09). These exciting findings provide strong rationale for larger randomized phase III studies that may validate these findings and allow a better understanding of which subgroups of patients are most likely to benefit from local therapies for oligometastases. An example of such a study is NRG-BR002, a randomized phase II/III clinical trial that is testing the benefit of SBRT above systemic therapy for oligometastastic breast cancer patients (32).

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Table 1:

Patient Characteristics

	Level II (4.0 Gy/fx) (n=8)	Level III (4.5 Gy/fx) (n=7)	Level IV (5.0 Gy/fx) (n=8)
Age (years)			
Median	59.5	52	73
Min - Max	54 – 85	42 – 74	30 – 79
Sex			
Male	4 (50.0%)	3 (42.9%)	4 (50.0%)
Female	4 (50.0%)	4 (57.1%)	4 (50.0%)
Race			
Asian	0 (0.0%)	1 (14.3%)	1 (12.5%)
White	8 (100.0%)	6 (85.7%)	6 (75.0%)
Unknown	0 (0.0%)	0 (0.0%)	1 (12.5%)
Zubrod Performance Status			
0	5 (62.5%)	6 (85.7%)	5 (62.5%)
1	3 (37.5%)	1 (14.3%)	3 (37.5%)
Number of Measurable Lesions			
1	4 (50.0%)	5 (71.4%)	5 (62.5%)
2	1 (12.5%)	2 (28.6%)	1 (12.5%)
3	3 (37.5%)	0 (0.0%)	2 (25.0%)
Size of Largest Lesion			
>1–3 cm	4 (50.0%)	5 (71.4%)	4 (50.0%)
>3–4 cm	1 (12.5%)	0 (0.0%)	1 (12.5%)
>4–5 cm	1 (12.5%)	1 (14.3%)	1 (12.5%)
>5–8 cm	2 (25.0%)	1 (0.0%)	2 (25.0%)
Site of Primary Tumor			
Colon/colorectal	3 (37.5%)	3 (42.9%)	2 (25.0%)
Breast	3 (37.5%)	2 (28.6%)	2 (25.0%)
Leiomyosarcoma	0 (0.0%)	1 (14.3%)	1 (12.5%)
GE Junction	1 (12.5%)	0 (0.0%)	0 (0.0%)
Liver	1 (12.5%)	0 (0.0%)	0 (0.0%)
Pancreas	0 (0.0%)	0 (0.0%)	1 (12.5%)
Pharyngeal	0 (0.0%)	1 (14.3%)	0 (0.0%)
Prostate	0 (0.0%)	0 (0.0%)	1 (12.5%)
Upper GI: esophagus	0 (0.0%)	0 (0.0%)	1 (12.5%)

Q1 = first quartile; Q3 = third quartile

Abbreviations: Gy, Gray; fx, fraction; GE, Gastroesophageal; GI, Gastrointestinal

Table 2:

Radiation Therapy Plan Central Review

	Level II (4.0 Gy/fx) (n=8)	Level III (4.5 Gy/fx) (n=7)	Level IV (5.0 Gy/fx) (n=8)
Tumor volume contouring score			
Per protocol	7 (87.5%)	7 (100.0%)	6 (75.0%)
Acceptable variation	1 (12.5%)	0 (0.0%)	2 (25.0%)
Unacceptable variation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Organs at risk contouring score			
Per protocol	8 (100.0%)	6 (85.7%)	6 (75.0%)
Acceptable variation	0 (0.0%)	0 (0.0%)	1 (12.5%)
Unacceptable variation	0 (0.0%)	1[a] (14.3%)	1[b] (12.5%)
Tumor volume dose score			
Per protocol	8 (100.0%)	6 (85.7%)	5 (62.5%)
Acceptable variation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unacceptable variation	0 (0.0%)	1[a] (14.3%)	3[c,d,e] (37.5%)
Organs at risk dose score			
Per protocol	8 (100.0%)	6 (85.7%)	8 (100.0%)
Acceptable variation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unacceptable variation	0 (0.0%)	1[a] (14.3%)	0 (0.0%)

Abbreviations: Gy, Gray; fx, fraction

[a]No small bowel contour; maximum dose was slightly high; and the liver dose was too high.

[b]No small bowel contour.

[c,d,e]Liver dose was too high; another patient did not have IV contrast so the gross tumor target volume could not be assessed accurately; one patient had one lesion treated to 35 Gy (not evaluated for protocol) and another to 50 Gy.

Table 3:

Dominant PTV, PTVs Combined, and Organs at Risk [Doses are in 10 fractions]

		n	Median	Min	Max
Dominant PTV	Volume (cc)	22	98.2	22.8	437.8
	D95 (Gy)	22	44.4	34.0	57.6
	D99 (Gy)	22	42.7	33.1	55.0
	% volume receiving ≥ dose reported on the CRF (35 to 50 Gy)	22	97.2	37.9	100.0
PTVs Combined[†]	Volume (cc)	22	73.3	22.8	437.8
	D95 (Gy)	22	43.8	34.0	57.1
	D99 (Gy)	22	42.0	33.1	55.0
	% volume receiving ≥ dose reported on the CRF (35 to 50 Gy)	22	93.6	38.5	100.0
Liver minus GTV	Volume (cc)	22	1421.8	935.5	3394.3
	Dmean (Gy)	22	14.6	2.1	27.3
	D700cc (Gy)	22	9.7	0.2	23.2
	D700cc (spared) (Gy)	22	8.1	0.2	38.8
	% Volume of the normal liver getting ≥ 27 Gy	22	21.5	2.0	48.2
	% Volume of the normal liver getting ≥ 24 Gy	22	26.2	2.5	53.6
Small Bowel	D0.5cc	18	19.7	0.4	37.8
	D5cc	18	14.4	0.3	31.7
	D25cc	18	3.0	0.0	24.5
Stomach	D0.5cc	21	19.7	0.7	39.6
	D5cc	21	18.8	0.3	34.6
	D25cc	21	16.6	0.2	29.3
Spinal Cord	Dmax	22	16.9	0.5	30.7
Kidney (bilateral)	Dmean	22	1.2	0.1	12.9

[†]The number of PTVs per patient range from 1 to 5 (see Table 1).

Abbreviations: PTV, planning target volume; cc, cubic centimeter; Gy, gray; CRF, case report form; GTV, gross tumor target volume

Table 4:

Dominant PTV and PTVs Combined by Dose Level [Doses are in 10 fractions]

			n	Median	Min	Max
Level II* (4.0 Gy/fx)	Dominant PTV	Volume (cc)	7	148.0	22.8	176.9
		D95	7	40.6	38.1	41.9
		D99	7	39.2	36.9	40.5
		% volume receiving ≥ 40 Gy	7	98.3	37.9	99.5
Level III (4.5 Gy/fx)	Dominant PTV	Volume (cc)	7	55.5	31.9	278.9
		D95	7	45.4	36.5	47.0
		D99	7	43.0	35.7	46.1
		% volume receiving ≥ 45 Gy	7	98.5	63.5	100.0
Level IV (5.0 Gy/fx)	Dominant PTV	Volume (cc)	8	90.6	27.9	437.8
		D95	8	49.4	34.0	57.6
		D99	8	47.8	33.1	55.0
		% volume receiving ≥ 50 Gy	8	92.5	52.3	100.0

* Data was never received for one patient on this dose level.

Abbreviations: Gy, Gray; fx, fraction; PTV, planning target volume

Table 5.

AE Summary (≥ grade 3)

	Level II (4.0 Gy/fx) (n=8) Grade			Level III (4.5 Gy/fx) (n=7) Grade			Level IV (5.0 Gy/fx) (n=8) Grade		
	3	**4**	**5**	**3**	**4**	**5**	**3**	**4**	**5**
Definitely, Probably, or Possibly Related to Protocol Treatment									
Worst hematologic	0	0	0	1	0	0	1	0	0
Worst non-hematologic	0	0	0	1	0	0	2	0	0
Worst overall	0	0	0	2	0	0	2	0	0
Lymphopenia	0	0	0	1	0	0	1	0	0
Diarrhea	0	0	0	1	0	0	0	0	0
Large Bowel Obstruction *	0	0	0	0	0	0	1	0	0
Enteritis	0	0	0	1	0	0	0	0	0
Colonic Hemorrhage *	0	0	0	0	0	0	1	0	0
Hyperglycemia	0	0	0	0	0	0	1	0	0
Any Relationship to Protocol Treatment									
Worst hematologic	0	0	0	1	0	0	1	0	0
Worst non-hematologic	1	0	0	1	1	0	2	0	0
Worst overall	1‡	0	0	2	1†	0	2	0	0

Abbreviations: Gy, Gray; fx, fraction

‡This was a patient with grade 3 ascites and encephalopathy unrelated to treatment.

†This was a small intestinal stricture unlikely related to treatment.

*This is the same patient.

Table 6:

Survival

	# Dead	Median Survival Time (Min-Max)
Level II (4.0 Gy/fx) (n=8)	8	29.9 months (11.4–43.1)
Level III (4.5 Gy/fx) (n=7)	6	31.5 months (22.5–62.8)
Level IV (5.0 Gy/fx) (n=8)	7	22.3 months (9.7–47.1)
All Patients (n=23)	21	24.1 months (9.7–62.8)

Abbreviations: Gy, Gray; fx, fraction