Original Article

Single-fraction image-guided extracranial radiosurgery for recurrent and metastatic abdominal and pelvic cancers: short-term local control, metabolic response, and toxicity

Charles L Perkins[1], Bassel El-Reyes[2], Edmund Simon[1], David Kooby[3], William Torres [4], John S Kauh[4], Charles A Staley[3], Jerome C Landry[1]

[1]Departments of Radiation Oncology, Emory University, Georgia, USA; [2]Department of Medical Oncology, Emory University, Georgia, USA; [3]Department of Surgical Oncology, Emory University, Georgia, USA; [4]Department of Radiology, Emory University, Georgia, USA

ABSTRACT

Purpose Extracranial radiosurgery (ECRS) is a novel treatment for inoperable recurrent or metastatic abdominopelvic cancers. However, local control, metabolic response, and acute toxicity remain undefined. We therefore analyzed these endpoints in patients treated with single-fraction image-guided ECRS at Emory University.

Methods 20 patients with recurrent or metastatic inoperable abdominal or pelvic cancers (23 sites) were treated with single-fraction ECRS using a Varian linear accelerator between 08/2006 and 02/2008. Patients with pancreas, biliary and liver cancer were part of an IRB-approved ongoing dose-escalation trial. 14 patients had received prior abdominal or pelvic external beam radiation. In 13 patients pre-treatment PET/CT was used to delineate the target volume. Image-guidance was provided by implanted fiducial markers and on-board imaging in 13 patients, and with cone-beam CT in 1 patient. 8 Patients were treated with respiratory gating. The median single-fraction dose delivered was 18 Gy. Each patient was assessed at 1 week, 1 month, and 3 months after radiosurgery for toxicity, and at approximately 1 month and 3 months with PET/CT for metabolic tumor response. Partial response was defined as a reduction in size of > 10% on CT and a decrease in maximum SUV of > 15% on PET. Complete response was defined as complete resolution on CT, and a reduction of SUV to background levels on PET.

Results The median follow-up was 6.3 months (range 1.5-12.2 months). The overall response rate (the sum of complete responses and partial responses) by treated site was noted in 36% (1 month), 47% (3 months) and 48% (final). A complete response was achieved in 13% (3 sites). At last follow-up, local control (sum of response rate and stable disease) was 74% . The metabolic response rate by pet only(sum of partial and complete responders) was 85% on final analysis. 23% of pet avid sites achieved a complete response. Two pet avid treated sites (13%) did show evidence of progression at 3 months, but subsequent CT/FDG-PET scans showed a decrease in maximum SUV; no patients suffered progressive disease based on metabolic imaging at last follow-up. Grade 1-2 upper GI acute toxicity (nausea, vomiting, gastritis, and pain) was noted in 47% and 55% of patients at 1 week and 1 month, respectively. Correspondingly, acute lower GI toxicity (diarrhea, pain) was lower at 12% and 6%. Overall grade 1-2 GI toxicity was seen in 59% of patients at 1 week (pain and nausea being the most common) and 61% of patients at 1 month post stereotactic body radiotherapy (SBRT) (nausea being the most common).

Conclusions Single-fraction image-guided ECRS for recurrent or metastatic abdominopelvic cancers is safe and effective in the short term. 3-month local control was very good , and was predicted by an early metabolic response as seen on PET/CT. Acute side effects were mild, with no patient experiencing grade 3 or greater toxicity. Dose escalation and long-term studies are warranted for this treatment approach.

KEY WORDS stereotactic body radiotherapy, pancreatic liver abdominal cancers. Single fraction sbrt, metabolic response toxicity

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Introduction

A recent theory proposes that not all metastatic disease is diffuse or systemic, and may be localized in number and anatomic location. In such cases of "oligometastases," durable response or potentially cure may be obtained with local therapy (1, 2). In fact, surgical series involving a number of sites including oligometastatic lung, liver, and adrenal have

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Correspondence author: Jerome C Landry, MD. Professor, Department of Radiation Oncology, Emory University. 1365 Clifton Rd. Atlanta 30138, GA, USA. Tel: 404-778-4469, Fax: 404-616-6380. Email: jland01@emory.edu.

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demonstrated the role of local treatment in such cases (3-6). Historically, however, such patients generally were not treated in a curative fashion, and most patients in this setting may not be surgical candidates for medical or anatomic reasons.

In addition, patients with local or regional recurrence of malignancy after primary treatment are generally deemed unsalvageable. Specifically, patients with abdomino-pelvic malignancies often have received a combination of surgery, local radiotherapy, and chemotherapy, which often precludes further local treatment for locoregional recurrence. However, as in the case with oligometastases, further local therapy for abdomino-pelvic recurrences may offer benefit in terms of local control and disease-free survival.

Technological advances have enabled the precise delivery of highly focused radiation doses to small areas, with minimal surrounding tissue exposure. Such techniques, termed stereotactic body radiotherapy (SBRT) or extracranial radiosurgery (ECRS), have demonstrated promising results in lung cancer (7-11), and for spinal metastases (12-15). In addition, phase I/II trials for primary liver malignancies and liver metastases have demonstrated a local control benefit, with acceptable toxicity (16-19). However, the majority of these regimens include fractionation involving 3 or greater treatments, while the effectiveness and toxicity of single and highly hypofractionated SBRT in the abdomen and pelvis remains largely unexplored, as well as the effectiveness of SBRT in the treatment of recurrent disease in this area.

We therefore undertook a retrospective analysis of patients with oligometastatic or recurrent or abdomino-pelvic tumors treated with hypofractionated (1-3 fractions) stereotactic body radiotherapy at Emory University between May 2006 and April 2008. Primary outcomes measured were local control and response rate, with secondary outcomes including acute toxicity and metabolic response.

Materials and methods

Patients

After obtaining IRB approval, the records of the Radiation Oncology department of the Emory Clinic were reviewed for patients who received hypofractionated stereotactic body radiotherapy for oligometastatic or recurrent pathologically-proven abdomino-pelvic malignancies. Twenty patients were identified, representing 23 individual anatomic targets treated between May 2006 and April 2008. Details identified included radiation treatment specifications, pre- and post-SBRT CT/ [^{18}F] fluorodeoxyglucose-positron emission tomography (FDG)-PET scans, serum liver function tests, and follow-up clinic exams. A Whole-Body Vaclock (Med-Tec), a device that immobilizes the patient by creating a rigid, conformal mold around the patient's body as well as utilizing straps around the patient, was used for each patient at the time of simulation. Next, a pancreatic protocol 3D CT scan was performed with the patient in the treatment position. If respiratory motion was anticipated, a 4D CT "gated" scan was performed using the Real-time Position Management system (Varian) and images were transferred to the 4D workstation (GE Medical) for motion analysis. The images from the CT scan (3D and/or gated) were then transferred from the workstation to the Eclipse Treatment Planning System (Varian) for stereotactic radiation planning.

Response analysis

The response rate and toxicity data were analyzed using Kaplan-Meier statistics. Response to treatment was determined by comparing pre-SBRT and post-SBRT CT and FDG-PET scans at various intervals after SBRT. Each scan was individually reviewed, and tumor size measurements were determined by an individual observer and compared to the official radiology report. Tumor size on CT was determined by the product of the maximal orthogonal diameters. Maximum SUV values were based on the official report. Definitions of response were based on a combination of RECIST criteria and the revised lymphoma response criteria (20-22). *Complete Response (CR)* = complete resolution of FDG activity (to background levels) on PET with no increase in size on CT. *Partial Response (PR)* ≥ 30% decrease in diameter product of lesion on CT, with no increase in mean SUV on FDG-PET; or >10% decrease in mean SUV on PET with no increase in diameter product of lesion on CT. *Progressive Disease (PD)* ≥ 25% increase in diameter product of lesion on CT, or >10% increase in mean SUV on FDG-PET. *Stable Disease (SD)* = does not meet criteria for CR, PR, or PD. *Local Control (LC)* = (CR + PR + SD).

Follow-up clinical visits at 1 week and 1 month were used to asses for acute symptomatic toxicity. Acute GI toxicity was scored based on the Common Terminology Criteria for Adverse Events version 3.0. For patients with liver metastases, or those patients with target volumes encompassing any portion of the liver, serum liver function tests (AST, ALT, and alkaline phosphatase) were drawn pre- and post-SBRT at 1 week and 1 month per a related institutional phase I dose escalation protocol. Liver toxicity was graded according to the RTOG Cooperative Group Common Toxicity Criteria.

Results

Treatment characteristics

All patients were treated at the Emory Clinic with

hypofractionated stereotactic image-guided body radiotherapy using a Varian Trilogy linear accelerator. Treatment details listed by disease site are described in Table 1. Prior radiation therapy was delivered to the treated area in 40% of patients, and 30% of patients received post-SBRT chemotherapy for at least one cycle. The target volume for radiotherapy was delineated by the fusion of the simulation CT scan with pre-treatment diagnostic CT or CT/FDG-PET imaging, to encompass the gross tumor volume (GTV) on CT or volume with SUV > 3.5 units (body weight) on FDG-PET. A planning target volume (PTV) was constructed by adding a custom 2-5mm margin radially around the GTV. Respiratory gating with a 4-D CT simulation was performed with 9 treated sites (39%). Radiation was delivered in a single fraction (87% sites), or fractionated over 2 to 3 treatments, each at least 3 days apart. Isodose lines of typical treatment plan for a metastatic colon adenocarcinoma lymph node treated with one fraction is depicted in Figure 1.

For image guidance, the interventional radiology service implanted radio-opaque fiducial markers in close proximity to

Table 1 Patient characteristics

Characteristic	n
Site	
Recurrent/metastatic colorectal carcinoma	7
Liver metastases	3
Recurrent/metastatic biliary carcinoma	4
Recurrent/metastatic pancreatic adenocarcinoma	3
Recurrent/metastatic jejunal adenocarcinoma	2
Recurrent esophageal carcinoma	2
Recurrent leiomyosarcoma	2
Age	
Median	57.5
Range	33-83
KPS	
Median	90%
Prior RT	
# of Patients (%)	8 (40)
Range (Gy)	44-55.8
Post-treatment chemotherapy	
# of Patients (%)	6 (30)

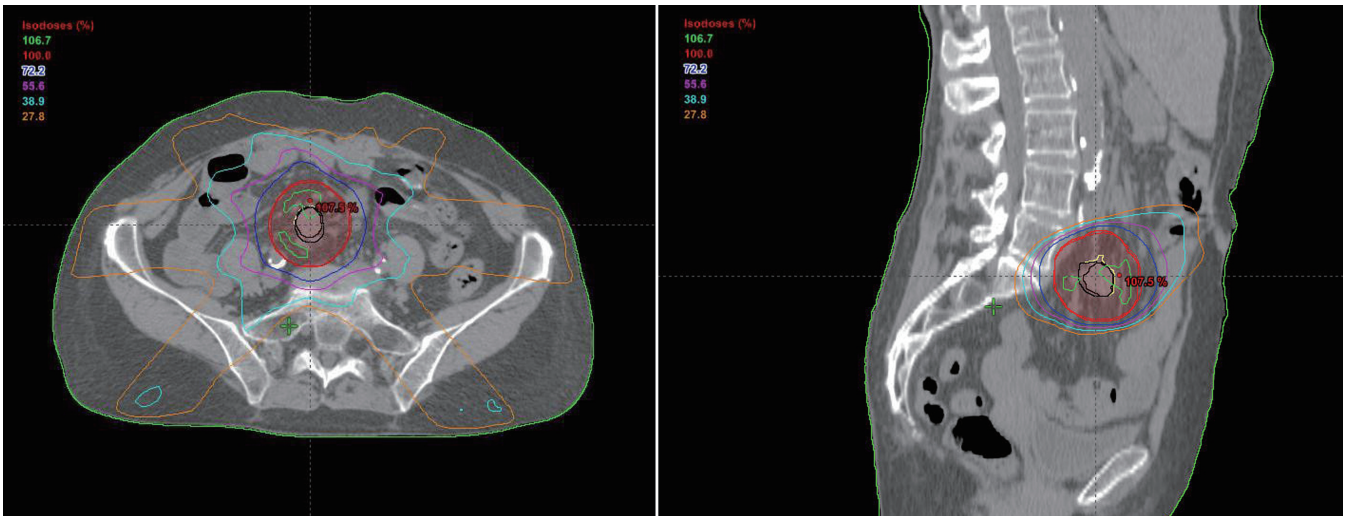


Figure 1 Isodose lines of typical treatment plan for a metastatic colon adenocarcinoma lymph node treated with one fraction

Table 2 Treatment characteristics

Dose range by site	
Recurrent/metastatic colorectal carcinoma	18-25 Gy
Liver metastases	15-25 Gy
Recurrent/metastatic biliary carcinoma	10-20 Gy
Recurrent/metastatic pancreatic adenocarcinoma	10-20 Gy
Recurrent/metastatic jejunal adenocarcinoma	15 Gy
Recurrent esophageal carcinoma	15-16 Gy
Recurrent leiomyosarcoma	17-18 Gy
Median dose	18 Gy
Fractionation	
Single Fraction	87%
2 Fractions	4%
3 Fractions	9%
Image-guidance	
Fiducial Markers	78%
Cone Beam CT	13%
Respiratory gating	39%

Table 3 Overall response

Outcome	1 month	3 months	Final
Complete response (CR)	9%	18%	13%
Partial response (PR)	27%	29%	35%
Response rate (CR + PR)	36%	47%	48%
Stable disease (SD)	45%	29%	26%
Progressive disease (PD)	18%	24%	26%
Local control	81%	76%	74%

Complete response = complete resolution of FDG activity (to background levels) on PET with no increase in size on CT.
Partial response ≥ 30% decrease in diameter product of lesion on CT, with no increase in mean SUV on PET; or >10% decrease in mean SUV on PET with no increase in diameter product of lesion on CT.
Progressive disease ≥ 25% increase in diameter product of lesion on CT, or >10% increase in mean SUV on PET.
Stable disease = does not meet criteria for CR, PR, or PD.
Local control = (CR + PR + SD).

the tumor target in 18 (78%) sites. At the time of treatment, these markers were utilized as on-board imaging targets for kv-kv image matching, incorporating respiratory gating as appropriate. Of the remaining 5 treated sites, image guidance was performed by cone beam CT at the time of treatment in 3 cases. Treatment setup was confirmed in the final 2 sites by bony kv-kv image matching. A summary of treatment characteristics is listed in Table 2.

Treatment response and local control

Treatment response based on CT & FDG-PET imaging at 1 month, 3 months, and last follow-up is presented in Table 3, with a median follow-up of 6.3 months after SBRT (range 1.5-12.2 months). The overall response rate (the sum of complete responses and partial responses) by treated site was noted in 36% (1 month), 47% (3 months) and 48% (final). A complete response was achieved in 13% (3 sites). At last follow-up, local control (sum of response rate and stable disease) was 74% (Tab 3, Fig 2). Table 4 lists local control by specifically grouped treatment sites.

Metabolic response

Pre-and post-SBRT evaluable CT/FDG-PET scans were available for review in 39% of treated sites. Based on

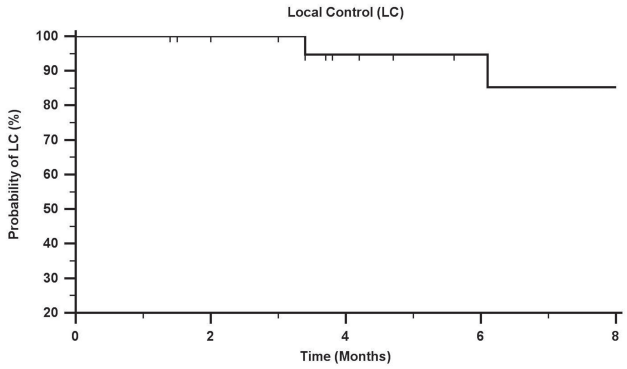


Figure 2 Local control

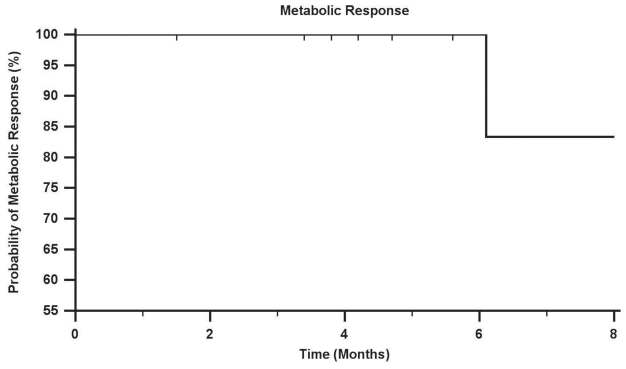


Figure 3 Metabolic response rate

Table 4 Local control by site

Site	*n*	1 month LC (%)	3 month LC (%)	Final LC (%)
Recurrent/metastatic colorectal carcinoma	7	71	43	57
Liver metastases	3	100	100	100
Recurrent/metastatic biliary carcinoma	4	75	75	75
Recurrent/metastatic pancreatic adenocarcinoma	3	67	100	100
Recurrent/metastatic jejunal adenocarcinoma	2	100	50	0
Recurrent esophageal carcinoma	2	100	100	100
Recurrent leiomyosarcoma	2	100	100	100
Local control	23	81%	76%	74%

Local control = RR + SD

Table 5 Metabolic response

Outcome	1month	3 months	Final
Complete response (CR)	18%	25%	23%
Partial response (PR)	73%	38%	62%
Response rate (CR + PR)	91%	63%	85%
Stable disease (SD)	9%	25%	15%
Progressive disease (PD)	0%	13%	0%

Complete response = complete resolution of FDG activity (to background levels).
Partial response ≥ 10% reduction in mean SUV (standard uptake value).
Progressive disease ≥ 10% increase in mean SUV.

maximum reported SUV, the metabolic response rate (sum of partial and complete responders) was 85% on final analysis (Tab 5, Fig 3). 23% of sites achieved a complete response. Two treated sites (13%) did show evidence of progression at 3 months, but subsequent CT/FDG-PET scans showed a decrease in maximum SUV; no patients suffered progressive disease based on metabolic imaging at last follow-up.

Acute GI toxicity

Acute symptomatic toxicity was evaluated based on scheduled 1 week and 1 month clinical exam follow-up visits (Tab 6). Grade 1-2 upper GI acute toxicity (nausea, vomiting, gastritis, and pain) was noted in 47% and 55% of patients at 1 week and 1 month, respectively. Correspondingly, acute lower GI toxicity (diarrhea, pain) was lower at 12% and 6%. Overall grade 1-2 GI toxicity was seen in 59% of patients at 1 week (pain and nausea being the most common) and 61% of patients at 1 month post SBRT (nausea being the most common). Although not reported in the manuscript, acute upper and lower GI toxicity resolved by 3 months post radiosurgery.

Table 6 Acute toxicity

Toxicity	Type	1 week	1 month
Upper GI	n/v, gastritis, pain	47%	55%
Grade 1		29%	22%
Grade 2		18%	33%
Grade 3+		0%	0%
Lower GI	diarrhea, pain	12%	6%
Grade 1		6%	6%
Grade 2		6%	0%
Grade 3+		0%	0%
	Overall GI Grade 1	35%	28%
	Overall GI Grade 2	24%	33%
	Overall GI Grade 1-2	59%	61%
	Overall GI Grade 3+	0%	0%

Table 7 Acute liver toxicity

Toxicity	Type	1 week	1 month
Grade 1	LFT's $\leq$ 2.5 X N	0%	0%
Grade 2	LFT's 2.6-5.0 X N	14%	29%
Grade 3+	LFT's > 5.0 X N	0%	0%

n = 7; LFT's = AST, ALT, alkaline phosphatase; N = baseline pre-ECRS serum level

Liver toxicity

In 7 patients (7 sites), the treated volume encompassed a portion of the liver. Based on pre- and post-SBRT serum LFT's (AST, ALT, alk phos), only 1 patient (14%) suffered Grade 2 toxicity at 1-week, and 2 patients (29%) experienced grade 2 toxicity at 1-month (Tab 7). No patients suffered grade 1 or grade 3+ liver toxicity at last follow-up.

Discussion

In this retrospective review, we report on the outcome of patients treated with hypofractionated image-guided stereotactic body radiotherapy for oligometastatic and recurrent abdomino-pelvic malignancies at the Emory Clinic. In the 20 patients treated (23 individually treated sites), with a median follow-up of 6.3 months, local control was 74%. Local failures tended to occur within the treated area (encompassed by the PTV), and did not indicate "marginal misses." 30% of the patients on this study did receive post-SBRT systemic chemotherapy, though the majority of these cases were in patients who showed evidence of progression after SBRT. Historically, this local control value is somewhat less than that expected by cranial radiosurgery (23, 24), although in the majority of cases no other local treatment options were available for the patients in this study. The doses in this study ranged from 15-25 Gy, the majority delivered in a single fraction. These single-fraction treated patients were part of an institutional dose escalation protocol, while those patients that received 2 or 3 fractions had previously received external beam radiotherapy in the treated area. As toxicity was relatively mild (discussed below), this may indicate room for dose escalation and or investigation of hypofractionation over 2-3 treatments in order to deliver a higher effective dose. A recent phase I study of SBRT for HCC-IHC has been reported, with dose hypofractionation over 6 treatments to 24-54 Gy (mean 36 Gy), with acceptable toxicity (19). Currently there is an ongoing RTOG phase I SBRT study for liver metastases, incorporating 10 fractions (28).

Although there has been a recent trend to treat cranial radiosurgery with a frameless setup, the majority of SRS treatments are still performed with a stereotactic head frame. Cranial SRS treatment also has the advantage of a relatively immobile intrafraction target. For cases in the abdomen, in order to reduce the setup PTV margin, potentially reduce surrounding tissue dose, and achieve the same precision as SRS, image-guidance should be an essential component of abdomino-pelvic radiosurgery. In this series, the majority of patients' setup was verified at the time of radiosurgery with radio-opaque markers implanted at the periphery of the target. These markers, along with bony anatomy, were used for on board imaging using kv-kv image matching.

This procedure, which typically involved the placement of 3 markers, was performed by interventional radiology and no complications were reported its use. For those patients who refused the implantable markers, or whose placement was deemed to encompass excessive procedural risk, image guidance was performed with cone beam CT for soft tissue matching.

Significant intrafraction respiratory motion for targets in the upper abdomen has been demonstrated (25). While this motion may have a moderate effect of daily fractionated treatment, the uncertainty imposed by this organ motion could potentially compromise target coverage with relatively tight PTV margins. In order to maintain a small PTV margin and reduce normal tissue toxicity for lesions in the upper abdomen, respiratory motion should be accounted for in the radiosurgical treatment of these lesions. In this series, patients with targets in the upper abdomen (pancreas, liver, small bowel) were simulated with a 4D-CT, and planned and treated at end expiration. The use of implanted fiducial radio-opaque markers has the added advantage of matching these markers with respiration using real time on board imaging to verify treatment location and respiration. While cone beam CT has the advantage of soft tissue matching, at least at our clinic, we have not been able to incorporate this technology with respiratory gating for treatment. As such, cone beam CT was reserved for lower abdomen/pelvic targets, or those patients who could not receive the implanted fiducial markers.

Using a combination of RECIST and the updated lymphoma response criteria(20-22), the overall response rate in this series was 48%. This value is a sum of the complete responders and partial responders, and incorporates the change in the diameter product on CT as well as change in maximum SUV on FDG-PET. Using the same criteria, the rate of disease progression at the treated site was 26%. Early response (PR or CR at 1-month) appeared to correlate with a durable response, as 84% of those patients with an early treatment response maintained local control at last follow-up. In addition, the based on change in maximum SUV on FDG-PET, the metabolic response rate was 85%, suggesting a strong functional response to the radiosurgery. Furthermore, no patients evaluable in this fashion showed evidence of metabolic progression after treatment. In other studies and observations, a "flare" phenomenon has been reported, in which there may be a transient increase in metabolic activity as measured by FDG-PET, followed by a reduction in metabolic activity (26, 27). This is thought to be most likely due to an inflammatory reaction. However, only 2 treated sites (both in the same patient) exhibited this phenomenon in our series, with a transient increase in maximum SUV at 3 months, followed by reduction in values to a point lower than that seen on the pre-SBRT FDG-PET scan.

Mild acute gastrointestinal toxicity was common in our study, both at 1 week (59%) and 1 month (61%) follow-up; however, no patient experienced grade 3 or greater gastrointestinal toxicity. Among those patients with symptoms, the most common symptoms were pain (58%) and nausea (50%). These were relatively well controlled with supportive medication. At longer follow-up, these symptoms tended to resolve (data not reported). One patient who received a single fraction of 25 Gy did develop a grade 2 gastric ulcer, which was managed conservatively with medication only. As part of a related institutional phase I dose escalation protocol, seven patients received radiosurgery within or adjacent to the liver parenchyma. Two patients experienced grade 2 liver toxicity, with an elevation alkaline phosphatase over pre-SBRT levels. Both of these patients also experienced locoregional disease progression with biliary obstruction, which may have contributed to the elevation in LFT's. No other patients experienced measurable liver toxicity.

In this retrospective series, the use of hypofractionated image-guided stereotactic body radiotherapy (extracranial radiosurgery) for oligometastatic and recurrent abdomino-pelvic malignancies resulted in excellent short-term local control rates, with frequent but mild acute toxicity. The short-term response rate was also excellent, as was metabolic response as measured by FDG-PET. Although a single fraction treatment offers certain logistic advantages, there may be room for improved local control with dose escalation or further fractionation, as treatment toxicity was relatively mild. There may also be a benefit for treatment of gastrointestinal malignancies in the primary curative setting, with dose escalation boosts to a small treatment area. While longer follow-up studies are warranted, for patients without other local therapy options, these results suggest that this type of radiosurgery may offer a significant clinical benefit.

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