Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

A prospective study of the safety and efficacy of liver stereotactic body radiotherapy in patients with and without prior liver-directed therapy

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ARTICLE INFO

Article history:
Received 7 November 2017
Received in revised form 27 December 2017
Accepted 2 January 2018
Available online xxxx

Keywords:
Hepatocellular carcinoma
Liver metastasis
Stereotactic body radiotherapy

ABSTRACT

Background and purpose: To evaluate the safety and efficacy of liver stereotactic body radiotherapy (SBRT), and examine potential factors impacting outcomes including prior liver-directed therapy.
Materials and methods: Patients with ECOG 0–1, Child-Pugh Class A or B, and primary hepatocellular carcinoma (HCC) or liver metastases unsuitable for surgical resection or ablation were eligible for a prospective single arm trial. SBRT was delivered with a CyberKnife system to 45 Gy in 3 fractions with a predetermined dose de-escalation scheme. Adverse events, local control, and survival were assessed.
Results: A total of 30 patients were enrolled. Eleven patients (37%) had HCC and 19 (63%) patients had liver metastases. Fourteen patients (47%) had prior liver-directed therapies including nine with liver resection, seven with trans-arterial chemoembolization, and six with radiofrequency ablation. Cumulative grade 2 and 3 acute toxicity occurred in 47% and 7% of patients, respectively. Similar rates of ≥grade 2 acute toxicity were observed between patients who had prior liver-directed treatments and those who did not. At a median follow-up of 12.7 months, 1-year local control and overall survival were 81% and 62%, respectively. Prior liver-directed therapy did not affect local control or survival.
Conclusions: Liver SBRT is a safe and effective treatment even in the setting of prior liver-directed surgical and ablative therapies.
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Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide, and the age-adjusted incidence rates have more than tripled in the past several decades in the United States [1,2]. In addition, the liver is a common site of metastases in multiple primary cancers including colorectal cancer. Although early stage HCC is potentially curable with surgical resection or a liver transplant, a minority of newly-diagnosed patients are eligible for a curative approach secondary to performance status, comorbidities, extent of disease, or hepatic reserve in the setting of underlying liver disease [3]. Similarly, complete surgical resection may yield long-term disease-free survival in patients with liver metastases, especially in the oligometastatic setting with a colorectal primary [4–6], but this approach is limited to a relatively small subset of patients.

Patients who are not candidates for surgical management have traditionally received ablative procedures (radiofrequency ablation [RFA], microwave ablation, etc.) or local arterial embolization [7]. More recently, technological advances in radiotherapy including stereotactic body radiotherapy (SBRT) and image guidance have enabled delivery of highly conformal radiation with "ablative" doses to the target (liver lesion) while providing good sparing of normal tissue (surrounding normal liver). Liver SBRT delivered in 1–5 fractions has become a viable treatment option in both primary and metastatic settings. Although no prospective randomized data exist on the effectiveness of SBRT compared to other ablative or embolization techniques, SBRT has potential advantages as it does not depend on the blood flow to the region of interest or location within the tumor for access. In addition, for larger lesions (≥2 cm), SBRT may have improved local control compared to RFA [8].

SBRT has been investigated prospectively for both primary HCC and liver metastases with excellent local control rates [9–26]. Many of the studies included a relatively small proportion of patients with prior liver-directed therapies such as resection, ablation, and/or embolization. Given the prevalence of prior local treatments to the liver in patients evaluated for liver SBRT, outcomes for these patients are clinically relevant and important to consider. This prospective study was designed to evaluate the safety and efficacy of liver SBRT, and examine potential risk factors that may impact outcomes including prior liver-directed therapy.

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https://doi.org/10.1016/j.radonc.2018.01.004
0167-8140/

Materials and methods

Patients

Patients with HCC or liver metastases, at least one, and up to three, measurable liver lesions, ECOG performance status 0–1, Child-Pugh Class A or B, and not candidates for surgical resection, RFA, or microwave ablation secondary to tumor location, hepatic function, or other medical/personal reasons were enrolled on a prospective single-arm protocol (NCT01528878). Enrollment on the protocol was prioritized over transarterial chemoembolization (TACE). Liver lesions of any size were eligible as long as radiation dosimetric parameters as outlined below were met. Patients also had to have adequate bone marrow and renal function including absolute neutrophil count $\geq$1000/mm^3, platelet $\geq$80,000/mm^3, and creatinine $\leq$2.0 mg/dL or creatinine clearance $\geq$45 mL/min. Patients with or without prior liver-directed therapies including surgical resection, RFA, and TACE were eligible. Patients with clinically apparent CNS disease and significant cardiovascular disease (defined as myocardial infarction or uncontrolled angina within 6 months, New York Heart Association Class III–IV congestive heart failure, or grade 3 cardiac valve dysfunction) were excluded to decrease potential confounders and to ensure necessary procedures including fiducial marker placement were able to be tolerated. The protocol was approved by the institutional review board and patients were enrolled following a written informed consent. Accrual, preliminary response, and toxicity data were reviewed by the Data and Safety Monitoring Committee on a semi-annual basis.

Treatment

RT was delivered with a CyberKnife system with tracking of liver motion using implanted fiducials. At least 3 fiducials were placed in the vicinity (within 6 cm) of the tumor in a non-colinear fashion by the interventional radiology team. Patients were simulated with a custom immobilization device (i.e. Alpha Cradle). Gross tumor volume (GTV) was delineated using contrast-enhanced MRI abdomen registered and fused with the contrast enhanced computer tomography (CT) scan taken on the radiation oncology simulator. GTV was expanded 8 mm supero-inferiorly and 5 mm radially for a combined clinical target volume (CTV) and planning target volume (PTV) expansion. Dose, fractionation, and dosimetric parameters were based on the patient's Child Pugh Class, a scoring system using five factors: total bilirubin, albumin, INR, presence of ascites, and encephalopathy (each scored using three tiers, +1, +2, and +3). Those with none and one abnormality have scores of 5 and 6, respectively, and are classified as Child Pugh Class A. Those with scores 7–10 are classified as Child Pugh Class B. Child Pugh Class A patients were treated to a total of 45 Gy in 3 fractions with a dose de-escalation scheme (in 2.5 Gy per fraction increments) to meet predetermined dose constraints: D35% of liver <15 Gy, at least 700 cc of liver <15 Gy, maximum dose to >1 cc of esophagus, heart, stomach, or small bowel <30 Gy, maximum dose to >1 cc of rib and chest wall <40 Gy, D50% of one kidney <14 Gy, and maximum point dose to spinal cord $\leq$15 Gy. Child Pugh Class B patients were treated with 35 Gy in 5 fractions with a predetermined dose de-escalation scheme (in 1.5 Gy per fraction increments) to meet predetermined dose constraints as above except a stricter liver constraint of D50% of liver <15 Gy. Dose was prescribed to the minimal isodose line that covered >95% of the PTV. Liver dose constraints were based on liver minus GTV volume.

Endpoints

The primary objective of the study was to assess tolerability of SBRT to the liver. Adverse events were graded by the Common Terminology Criteria for Adverse Events (CTCAE) v.3.0. Acute toxicity was evaluated during the first 3 months following therapy, and all subsequent toxicities were deemed late toxicity. Tolerability was based on hepatic toxicity including worsening liver function parameters, clinically apparent worsening of portal hypertension, new or worsening bleeding esophageal varices, or worsening ascites within the first 3 months from initiating SBRT. The trial was designed to stop early if the rate of $\geq$grade 2 hepatic toxicities exceeded 33% or the rate of any grade 3 toxicity plus two times the rate of grade 4 toxicity exceeded 40%. Secondary endpoints were local response, local control, and survival. Complete response (CR) was defined as disappearance of the target lesion, partial response (PR) as regression of measurable disease, progressive disease (PD) as increase by $\geq$50% in the product of the two perpendicular diameters of an irradiated lesion, and stable disease (SD) as all others not meeting criteria for CR, PR, or PD. Patients had scheduled follow-up 1 week post-RT, 4 weeks post-RT, 8 weeks post-RT, and every 3 months thereafter for up to 2 years or until disease progression in a treated liver lesion.

Statistical analysis

Local control and survival were assessed using the Kaplan–Meier method. Local control was also calculated using the cumulative incidence function to account for death as a competing risk. Post-hoc analyses using log rank tests were conducted to assess differences in local control and survival between subgroups. Univariable Cox proportional hazards regression was used to assess associations between patient or treatment characteristics and local control/survival. Post-hoc analyses using Chi-squared tests were conducted to compare toxicity outcomes between subgroups. All statistical analyses were done using Stata, version 14.2.

Results

Patient and treatment characteristics

A total of 30 patients were enrolled from June, 2009 to March, 2014 at two institutions. Patient and treatment characteristics are shown in Table 1. Eleven patients (37%) had primary HCC and 19 (63%) patients had liver metastases with a median age of 65.5. All but two of the 19 patients with liver metastases had a Child Pugh score 5, whereas 5 of the 11 patients with HCC had a Child Pugh score 5. Fourteen (47%) patients had prior liver-directed therapies including 9 (30%) with liver resection, 7 (23%) with TACE, and 6 (20%) with RFA. Among the 14 patients who received prior local treatment to the liver, 9 had more than one intervention, and of the 9 with prior liver surgery, 7 underwent resection of 2 or more segments, 4 of whom had a hepatic lobectomy.

Among the 30 patients, 28 received SBRT to a new lesion and 2 received SBRT for a local recurrence or failure to respond following TACE. Most patients (87%) received treatment to one lesion with a median size of 3.5 cm. The smaller lesions were almost entirely located centrally in the liver or near the hepatic dome as our institutional preference was to ablate smaller accessible lesions with RFA or microwave. Patients received a total dose of 27.5–45 Gy in 3–5 fractions per a predetermined de-escalation scheme with a median dose of 45 Gy in 3 fractions. Median volume of liver receiving $\leq$15 Gy was 1239 cc and mean liver dose was 10.3 Gy.

Toxicity

Cumulative acute toxicity was defined as toxicity occurring within 90 days of treatment initiation. Grade 2 and 3 toxicities possibly attributable to SBRT occurred in 14 (47%) and 2 (7%) of 30

Please cite this article in press as: Moon DH et al. A prospective study of the safety and efficacy of liver stereotactic body radiotherapy in patients with and without prior liver-directed therapy. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.01.004