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Original Research Article

Definitive radiation therapy for hepatocellular carcinoma with portal vein tumor thrombus

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ABSTRACT

Background: The purpose of this study is to review the results of radiation therapy (RT) for hepatocellular carcinoma (HCC) with portal venous tumor thrombus (PVTT) in a Western patient population.
Methods: Thirty-four patients with HCC PVTT treated from 2007 to 2014 with RT were identified. Biologically effective dose (BED) was calculated for each patient, and greater than the median dose delivered (75 Gray (Gy)) was evaluated as a potential prognostic factor. Survival was compared and independent prognostic variables were evaluated by a Cox proportional hazards regression model.
Results: Twenty-six patients (76.5%) exhibited a radiographic response to RT, and 10 patients (29.4%) ultimately developed local failure. Local control, liver control, distant control and OS at one year were 57.1%, 36.4%, 55.2% and 57.4%, respectively. Patients who received a BED >75 Gy had a significantly better local control at 1 year (93.3% vs 45.6%; Log Rank p = 0.0184). Patients who received a BED >75 Gy also had significantly better median survival (24.7mo vs 6.1mo) and 1-year overall survival (76.5% vs 30.0%) when compared with BED ≤75 Gy (Log-Rank p = 0.002).
Conclusion: Our data suggest that RT should be considered for well-selected patients with HCC and PVTT for the purpose of improving local control and potentially prolonging the time to worsening venous obstruction and liver failure. When feasible, dose-escalation should be considered with a target BED of >75 Gy if normal organ dose constraints can be safely met.

Introduction

Patients with hepatocellular carcinoma (HCC) can develop portal vein tumor thrombi (PVTT) due to direct extension or by intravascular metastases. The incidence ranges from 12 to 44% at the time of diagnosis [1,2]. Without treatment, patients with PVTT have a dismal prognosis with median survival rates of approximately three months [3], and fewer than one third of patients survive one year [4]. Currently, there is no consensus on how best to treat patients with HCC PVTT. United States [5] and European [6] guidelines recommend Sorafenib, while Asian consensus guidelines are more permissive of using locoregional treatments including surgical resection, radiation therapy (RT), transarterial chemoembolization (TACE), and radioembolization (RE) [7].

Initial concerns about radiation-induced liver disease (RILD) limited enthusiasm for RT in this patient population; however, as more data regarding dose-volume risk parameters become available [8–10], there has been increasing interest in the use of RT for patients with locally advanced or otherwise unresectable HCC, including those with PVTT [6,7,11]. Older studies suggested a potential, though modest, survival benefit with RT for these patients [12–17]. More recently, advanced radiation techniques such as proton beam radiation (PBR) [18,19], hypofractionated PBR [20] and stereotactic body radiotherapy (SBRT) [24,25] have been utilized for normal tissue sparing, effective dose-escalation or both.

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Most published studies have come from Asia, where there is a higher incidence of HCC [23]. However, the incidence of HCC is rising in Western countries given the increasing incidence of non-alcoholic steatohepatitis (NASH) [24]. To our knowledge, a dedicated investigation of definitive RT for HCC PVTT in a Western population has not been reported previously. Therefore, the purpose of this study was to evaluate the experience of a single institution in the use of radiation in the definitive treatment of HCC PVTT.

Methods

Patient selection

After institutional review board approval, we identified patients with pathologically or radiographically confirmed HCC with evidence of PVTT on ultrasonography or computed tomography (CT) treated with definitive EBRT at a single institution from 2007 to 2014. All patients were prescribed a Biologically Effective Dose (BED) of ≥45 Gy. The majority of patients received prior systemic therapy or liver-directed therapy with TACE or radiofrequency ablation; however, no patient received prior surgical intervention or prior radiation therapy. Concurrent sorafenib was sometimes given at the discretion of the treating medical oncologist with doses ranging from 200 mg daily to 400 mg twice daily.

Treatment

RT was delivered using either 3D conformal radiotherapy (3DCRT), intensity-modulated radiation therapy (IMRT), SBRT (≤5 fractions) or PBR based on physician preference. For patients receiving ≥50.4 Gy, daily image guidance included either daily CT-based alignment to soft tissue or kilovoltage xray-based alignment to liver fiducials in the inspiration breath-hold position [25,26]. For all patients, the gross tumor volume (GTV) was delineated using all available imaging and included the PVTT plus the primary liver tumor and any radiographically involved lymph nodes if feasible to treat without unacceptable additional toxicity. A clinical target volume (CTV) was created to encompass potential microscopic disease by expanding the GTV by 0–10 mm. The planning target volume (PTV) was created by adding a 0–5 mm margin to the CTV. A central simultaneous integrated boost (SIB) dose of 60–100 Gy (2.4–5 Gy per fraction) was delivered to a volume created by contracting the GTV by 1 cm and subtracting a 5 mm planning risk volume (PRV) expansion around adjacent organs-at-risk (OARs) for select patients. The final dose and fractionation regimen was ultimately decided by the treating radiation oncologist. Our institutional practice from 2007–2010 was typically to use dose and fractionation regimens yielding a BED </=75 Gy (50.4 Gy in 1.8 Gy fractions, 45 Gy in 3 Gy fractions or 50 Gy in 5 Gy fractions, for example). After 2010, patients were sometimes offered dose and fractionation regimens yielding a BED >75 Gy (75 Gy in 3 Gy fractions or 67.5 Gy in 4.5 Gy fractions or 50 Gy in 12.5 Gy fractions, for example). In addition to temporal trends in our practice pattern, patients typically offered the most aggressive regimen achievable while meeting predetermined dose-volume constraints (Table 1). Acute toxicities were collected weekly and graded per the National Cancer institute Common Terminology for Adverse Events (NCI CTCAE) version 4.

Data collection

Pretreatment clinical features and details regarding prior systemic and local therapies were collected. Total radiation dose delivered was recorded both as nominal dose as well as BED, which was calculated using an α/β ratio of 10. All living patients were followed until August of 2016, and outcome measures including local, liver and distant control were collected as was vital status at last follow-up. Patients with metastatic disease at the time of radiotherapy were excluded from the distant recurrence analysis.

Table 1
Dose constraints for organs at risk utilized when treating hepatocellular carcinoma related portal vein tumor thrombi by daily radiation fraction size.

Organ at risk	Dose constraint
1.8–2.5 Gray fraction size	
Liver minus GTV	Mean <28 Gy (<24 Gy if Child-Pugh B)
Stomach/Duodenum/Small Bowel	Maximum <54 Gy
3–4.5 Gray fraction size	
Liver minus GTV	Mean <24 Gy (<20 Gy if Child-Pugh B) 700 cc <24 Gy (<20 Gy if Child-Pugh B)
Stomach/Duodenum/Small Bowel	Maximum <45 Gy
≥5 Gray fraction size[*]	
Liver minus GTV	Mean <16 Gy 700 cc <15 Gy
Stomach/Duodenum/Small Bowel	Maximum <28 Gy

GTV = gross tumor volume, Gy = Gray.
[*] Stereotactic radiation regimens in 3–5 total fractions.

Statistical methods

Between-group comparisons were performed using the non-parametric Kruskal-Wallis test for continuous variables and the Pearson chi-square test for categorical variables. Survival times were calculated using the Kaplan-Meier methods from the point at which EBRT began. The log-rank test was used for statistical comparison of the survival curves for all potential variables. The Cox proportional hazards regression model was used by the forward stepwise method with all potential predictors with a $p < 0.2$ on univariate analysis were included in the multivariable model. Unadjusted P-values < 0.05 were considered to be significant. JMP® version 12 (SAS Institute Inc. Cary, NC) was used for all analyses.

Results

There were a total of 81 patients treated with RT for HCC between 2007 and 2014. Of these, 34 patients (42%) had PVTT confirmed on pre-radiation CT imaging. For these 34 patients included in this analysis, the median [range] follow-up was 12.8 [0.73–60.5] months. For patients alive at the time of the analysis, the median [range] follow-up was 18.7 [3.5–60.5] months. Patient characteristics are given in Table 2 and are separated by BED >vs ≤75 Gy (the median BED). Patients receiving a BED >75 Gy had a smaller gross tumor volume treated, received concurrent chemotherapy less often and received SBRT or PBR more often. Otherwise, baseline and treatment characteristics were similar.

Local control and patterns of recurrence

Local control at one year was 57.1%. Local recurrence was defined as an in-field or marginal failure. At the time of analysis, eight patients had developed a local recurrence. Six patients had tumor recurrence within the PTV volume, and the remaining two patients developed marginal recurrences. Of all the factors evaluated, only BED >75 Gy was associated with improved local control on univariate analysis (HR [95% CI] 0.21 [0.04–0.95]; $p = 0.043$) (Table 3).

Liver control at one year was 36.4%. At the time of analysis, 17 patients developed new metastatic lesions in the liver. Distant control at one year was 55.2%. Extrahepatic metastases ultimately developed in 18 patients, including nine patients with lung metastases, four patients with distant nodal metastases, two patients