Response and Overall Survival for Yttrium-90 Radioembolization of Hepatic Sarcoma: A Multicenter Retrospective Study

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Abstract

Purpose: To evaluate the effectiveness and safety of Y-90 transarterial radioembolization (TARE) for treatment of primary and metastatic soft tissue sarcoma (STS) of the liver.

Materials and Methods: A retrospective review of 39 patients with primary (n=2) and metastatic (n=37) hepatic STS treated with TARE at 4 institutions was performed. 14 STS subtypes were included, with leiomyosarcoma being the most common (51%). TARE with glass (22 pts) or resin (17 pts) microspheres was performed, with single lobe (17 pts) or bilobar treatment (22 pts) based on disease burden. Adverse events of treatment, overall survival (OS), and tumor response per RECIST criteria at 3, 6, and 12 months post embolization were assessed.

Results: 14 patients demonstrated either partial or complete response to therapy with an objective response rate of 36%. 30 patients (77%) demonstrated disease control (DC), demonstrating either stable disease or response to treatment. Median OS was 30 months (95% CI 12-43 months) for all patients. DC at 3 months was associated with an increased median OS (44 months) compared with disease progression (PD) (7.5 months; $p < 0.0001$). Patients with DC at 6 months also demonstrated an increased median OS (38 months) compared to those with PD (17 months; $p = 0.0443$). Substantial adverse events 1 liver abscess, 1 gastric ulceration, and 1 pneumonitis.

Conclusion: Patients with hepatic STS treated with TARE demonstrate a high rate of DC and median OS of 30 months, which suggests a role for TARE in the palliation of hepatic STS.

Introduction

Soft tissue sarcoma (STS) is a rare and diverse group of cancers consisting of over 50 separate subtypes, which comprises less than 1% of the malignancies diagnosed in the United states annually, and has a 60% 5 year

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metastasis free survival rate for early stage disease (1,2). Metastases from STS, however, frequently occur despite aggressive local treatment. Among the 85-88% of STS patients diagnosed with intermediate to high grade tumors, up to half will develop metastatic disease (1,3). Additionally, 8% of patients with STS initially present with metastatic disease (1,2). Prognosis for patients with metastatic soft tissue sarcoma is much poorer, with a median overall survival (OS) ranging from 12-17.4 months (2–7). Within this group, among the 18-19% of patients affected with liver metastases, the prognosis is even poorer, with a median OS of 11 months, and poorer response to chemotherapy(4,8). Primary hepatic STS demonstrates a similar prognosis for resectable disease with 5 year survival ranging from 36-72%. This survival decreases precipitously with nonresectable disease with a median OS of less than 12 months (9,10).

Yttrium-90 transarterial radioembolization (TARE) is an effective treatment for hepatocellular carcinoma (11), as well as for metastatic disease to the liver (12,13). There is little in the literature describing TARE for hepatic STS, with only a few case studies or mentions in multiple tumor type studies (11,12) The goal of this multi-center study was to assess the safety and effectiveness of TARE for hepatic STS.

Materials and Methods

Patients

This multi-institutional study was approved by the respective Institutional Review Boards of four participating institutions and conducted in compliance with the Health Insurance Portability and Accountability Act, and the need for informed consent was waived given the retrospective nature of the study. All patients with hepatic STS who underwent TARE from the date that radioembolic agents became available at the participating institutions were included. From 2006 to 2015, 39 patients with primary liver (n=2) or metastatic liver sarcoma (n=37) underwent TARE. A total of 14 different subtypes of STS were included in the study. Gastrointestinal stromal tumors, due to their response to imatinib and resulting improved OS, were excluded from the study. The patient characteristics are summarized in Table 1. At least 1 of chemotherapy had been received by 95% (37/39) of the patients prior to TARE. The most common first line therapies were doxorubicin monotherapy (n=5) and docetaxel

and gemcitabine (n=5). Second and third line chemotherapy regimens were variable, but most commonly included docetaxel and gemcitabine (n = 7), pazopanib (n=6), and doxorubicin (n=4).

Embolization Procedures

TARE procedures were performed by multiple interventional radiologists at their corresponding institutions, with proceduralist experience levels ranging from 11-23 years. At all institutions, patients underwent visceral arteriography with the administration technetium-99^{m}-macro-aggregated albumin, to estimate hepatopulmonary shunting, and to simulate dose to target liver. During subsequent TARE procedures, either glass (TheraSphere, BTG, London, UK) or resin (SirSphere, SIRTex, Sydney, Australia) Yttrium-90 microspheres were administered intra-arterially per physician preference. A summary of therapy characteristics are detailed in Table 2. Resin microspheres were administered in 17 patients, and glass microspheres were administered in 22 patients. Prophylactic coil embolization of nontarget arteries was performed in 20 patients prior to TARE. Twenty-two patients underwent bilobar treatment; 14 of these were performed as a single therapy, and 8 were performed as 2 staged treatments. Five patients underwent retreatment with TARE after disease progression.

Imaging Evaluation

Imaging evaluation varied based on patient characteristics, institutional protocol, and the imaging modality best demonstrating the patient's disease. All patients were evaluated with serial cross sectional imaging to evaluate for tumor response. The majority of patients were evaluated with serial CT scans (25 patients, 64%), with 4 (10%) patients evaluated by MRI follow up, and the remaining 10 patients (26%) were evaluated with a combination of CT and MRI or PET-CT. Imaging protocols were determined by institutional preference.

Assessment of Tumor Response

Evaluation of tumor response was performed based on imaging characteristics at 3 month, 6 month, and 12 month intervals post treatment. Due to different institutional imaging follow up protocols, there was some heterogeneity in the availability of imaging follow up data. Imaging follow up was available at 3 months, 6 months, and 12

months for 34/39 (87%), 29/39 (74%), and 12/39 (31%) patients, respectively. All patients, however, had imaging follow up available at either 3 or 6 months.

Assessment of tumor response was determined using the Response Evaluation Criteria in Solid Tumors v 1.1 (RECIST) strictly applied to the treated liver. (16) Grading of tumor response was separated by criteria into those demonstrating complete response (CR), partial response (PR), stable disease (SD), and progression of disease (PD), and are detailed in Table 2. Tumors demonstrating CR, PR, or SD were grouped together as disease control (DC) and compared with those demonstrating PD for the purposes of statistical analysis.

Adverse Events Evaluation

All patients had baseline laboratory evaluations prior to TARE. Toxicities from therapy were defined based on the Common Terminology Criteria for Adverse Events v 4.03. (17) These were assessed prior to treatment, as well at follow up appointments over a 3 month period. Clinical follow up at 3, 6, 9, and 12 month intervals was also performed. The assessments included clinical symptoms, complications of the embolization procedure, and laboratory value derangements.

Statistical Analysis

Frequencies were obtained for categorical variables, and mean and standard deviation were computed for continuous variables. Patient characteristics were also summarized based on embolization received. Embolization-group differences were assessed using ANOVA and Fisher's exact test. Overall survival was estimated using Kaplan-Meier method. Stratified analyses of survival were also performed for categorical covariates including dose to liver, study institution, and year of treatment. Median survival and respective 95% confidence interval were noted. Equality of survival across different covariate strata was tested using log-rank test. In cases where survival functions for different strata crossed, Fleming-Harrington test was performed. Survival analyses described were also repeated based on response status (PD vs DC) at 3 and 6 months follow-up. Statistical analyses were performed at the 0.05 alpha-level. All statistical analyses were conducted using SAS version 9.4.

Results

Adverse Events

Post-treatment toxicity information was available for 35 patients. The most common adverse events observed were fatigue, abdominal pain, thrombocytopenia, and elevation of alkaline phosphatase (Table 3). The majority (93%) of these observed AEs (n =136) were either Grade I (n=103) or Grade II (n=25). Grade 3 toxicities included elevation of bilirubin (n=1), hypoalbuminemia (n=1), and elevation of alkaline phosphatase (n=1). One patient with a history of prior right hepatectomy and hepaticojejunostomy developed a liver abscess 5 months after treatment despite antibiotic prophylaxis with moxifloxacin prior to and 3 weeks post-TARE, and was treated with percutaneous drainage and antibiotic therapy. One patient developed gastroduodenal ulceration secondary to nontarget embolization despite prophylactic coil embolization, secondary to anomalous reconstitution of the right gastric and gastroduodenal arteries via the cystic artery, and was successfully managed with medical therapy. One patient also developed a delayed cryptogenic organizing pneumonia 4 months post embolization, with flares of disease coinciding with chemotherapy administration, suggesting a radiation recall mechanism.

Response

Over 6 months of imaging post treatment, 1 patient demonstrated liver specific CR to therapy, and 13 patients demonstrated PR to therapy, with an objective response rate of 36%. 6 patients initially demonstrating SD at 3 months showed PR or CR at 6 month follow up imaging. An additional 16 patients demonstrated SD, with a total of 30 (77%) patients demonstrating stable disease or response to therapy. DC was seen in 16/22 patients (73%) treated with glass microspheres and 14/17 (82%) patients treated with resin microspheres at 6 months post treatment. Nine patients demonstrated PD, with 6 of these patients demonstrating enlarging target lesions, and 3 demonstrating new lesions within the treatment bed. Among the 12 patients with imaging available at 12 months, 5 demonstrated DC, and 7 demonstrated PD. Among patients retreated after disease progression, 80% (n=4) had demonstrated initial DC after treatment with late disease progression. After retreatment, 80% (n=4) demonstrated DC at 3 months, and 60% (n = 3) demonstrated DC at 6 months.

Survival

During a median follow up period of 22 months (Range: 1-87 months), 27 of 39 patients (69%) died. Median OS was 30 months (95% CI 12-43 months) (Figure 1). Several patients demonstrated long term survival with 11 patients (28%) demonstrating greater than 36 month survival and 2 patients (5%) demonstrating greater than 60 month survival. The percent surviving was 83% at 1 year, 61% at 2 years, 37% at 3 years, and 10% at 5 years. No statistically significant difference in OS was found based on year of treatment (p=0.66), radiation dose to the liver (p=0.58), or treatment institution (p=0.42).

The OS for patients with DC at 3 months was increased compared to those with PD (p <0.0001), with median OS of 44 months (95% CI 23-86 months) for patients with DC, and 7.5 months (95% CI 4-30 months) in patients with PD. (Figure 2) This difference in OS persisted at 6 months (p = 0.0443), with patients with DC demonstrating a median OS of 38 months (95% CI 23-49 months), compared to those with PD at 6 months with a median OS of 17 months (95% CI 12-30 months) (Figure 3).

Patients who underwent treatment with glass microspheres demonstrated an increased OS as compared to those treated with resin microspheres (p = 0.0278), with a median OS of 30 months (95% CI 12-39 months) for those treated with glass microspheres and 24 months (95% CI 5-56) for those treated with resin microspheres. (Figure 4) Radiation dose to the target liver was significantly higher for glass microspheres (mean 99.13 Gy ±39.9) as compared to resin microspheres (mean 45.56 ±16.65) (p=0.0004). No significant difference in the liver volumes was demonstrated between the two groups (p=0.14).

Discussion

Multiple methods of achieving local control of liver sarcoma have demonstrated varying levels of efficacy. Management with surgical metastectomy of limited disease has demonstrated a median OS post-resection ranging from 20-45 months, with the most important factor affecting survival being the amount residual disease at the time of surgery (18,19). Several studies have also demonstrated transarterial therapies as a viable option for treatment of nonresectable hepatic STS. Transarterial chemoembolization has been demonstrated as a viable means of controlling disease in the liver, with a recent study of 30 patients with STS metastatic to the liver demonstrating a median OS of 21.2 months (20). Two additional case series demonstrate varying levels of efficacy

for chemoembolization and bland embolization of STS metastases, with median OS ranging from 13 to 18 months (13,14). TARE of sarcomas has been reported in a few case reports and a small series of gastrointestinal stromal tumors, which suggest that this may also be useful in treating primary and metastatic hepatic STS (11,15,16). The feasibility of treatment of nonresectable primary hepatic STS with transarterial therapies has been demonstrated in several case reports and case series, with survivals in responders ranging from 8-12 months (16–18).

This study demonstrates promising results for patients with hepatic STS treated with TARE. A median OS of 30 months for STS metastatic to the liver represents a substantial increase in survival as compared to prior series demonstrating survivals ranging from 18-21 months treated with TACE or bland embolization (13,14,19). This also compares favorably to the median OS for patients with STS metastatic to the liver not managed with locoregional therapy, around 11 months(8). Unfortunately, due to the heterogeneity of the patient cohort as well as the variability in their treatments, definitive claims of the superiority of TARE cannot be made. However, in the context of other studies demonstrating the survival benefit of patients treated with transarterial therapies, the results of this study suggest that TARE should be considered as a means of prolonging survival in patients with liver dominant STS.

The survival benefit was more pronounced in patients who demonstrated disease control after the initial treatment, as compared to those who progressed despite treatment. This stratification between responders and nonresponders has been seen with other tumors treated with TARE (20,21). Late progression of disease on follow up imaging appeared to be predominantly from new liver metastases, as opposed to growth of treated lesions. The high rate of disease control in patients undergoing repeat embolization following late progression suggests that retreatment may also be appropriate in patients with subsequent disease progression after initial favorable response to treatment.

The majority of the patients in this study had extrahepatic metastatic disease as well, which has worsened survival as compared to those with liver only disease (8). Subjectively, in patients with 12 month or greater post-treatment imaging, these patients demonstrated progression of extrahepatic disease despite response to treatment of their liver metastases post TARE. As has been noted, selection of patients most likely to benefit from TARE is important

(22). This cohort was selected for TARE because they demonstrated liver dominant disease. The efficacy of TARE for treatment of hepatic STS cannot be generalized to patients with significant extrahepatic disease.

The difference in median OS in patients treated with glass microspheres compared to those treated with resin microspheres is of uncertain clinical implication. Although a significantly increased radiation dose was seen with glass microspheres as compared to resin microspheres, subgroup analysis did not determine radiation dose by itself to be statistically significant for OS, and there is substantial overlap in the confidence interval. Although the results suggest that glass microspheres are superior to resin microspheres for treatment of STS metastatic to the liver, given the small size of the patient cohort, this study is likely statistically underpowered to make definitive conclusions.

The toxicity profile experienced by the patients receiving TARE was low, and consistent with prior studies(23). The development of a hepatic abscess in 1 patient is a known complication of transarterial therapies in those with altered biliary anatomy, and can occur, as did in this case, despite antibiotic prophylaxis (24). Gastroduodenal ulceration due to off target embolization can occur in up to 3.2% of TARE procedures and can occur despite attempts at prevention (27). The complication of pneumonitis was not a conventional radiation pneumonitis, but rather a radiation recall pneumonitis, which occurred at a lung dose less than 30 Gy, the conventional cutoff for TARE. Radiation recall phenomenon is a condition in which an inflammatory response is induced by drug therapy, most commonly chemotherapy, in previously irradiated tissue, and can occur at doses as low as 10 Gy (25). These more substantial toxicities underline the fact that while TARE is well tolerated in most patients, it is not an entirely benign procedure. The overall toxicity profile, however, does compare favorably with that of the most commonly used chemotherapy lines used for treatment of STS (4), in which grade III and grade IV toxicities can affect up to 46% of patients treated with combination therapy.

There are several limitations to this study which are related to the heterogeneity of the cohort, treatments, and participating institutions. Due to the multi-institutional nature of the study, differences in patient selection and procedural technique are inherently present. Second, imaging response was performed for the treated liver only, whereas assessment of response to systemic therapy is based on overall RECIST criteria. Due to the rarity of STS

being treated, there is also considerable heterogeneity in STS subtypes. The accuracy of assessing tumor response after transarterial therapy using RECIST criteria is another limitation, and the difficulty of using RECIST criteria for STS has been previously reported (19). Additionally, there is the potential for bias related to patient selection, both by referring oncologists and treating interventional radiologists based on which patients they thought would be most likely to benefit from and tolerate TARE. The presence of concurrent systemic chemotherapy in these patients may also confound the results of the study.

In conclusion, patients with hepatic STS demonstrated a median 30 month OS after TARE with a favorable side effect profile and 36% response rate. These results suggest that TARE can be considered as a possible palliative treatment for patients with liver dominant disease.

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Figure Legends

Figure 1: Kaplan-Meier curve of survival for all patients after TARE

Figure 2: Kaplan-Meier curve of survival after TARE for patients with disease control (DC) at 3 months as compared to those with disease progression (PD) ($p<0.0001$).

Figure 3: Kaplan-Meier curve of survival after TARE for patients with disease control (DC) at 6 months as compared to those with disease progression (PD) ($p<0.0443$).

Figure 4: Kaplan-Meier curve of survival after TARE for patients treated with glass microspheres versus resin microspheres (PD) ($p<0.0278$).