CLINICAL STUDY

Long-Term Toxicity after Transarterial Radioembolization with Yttrium-90 Using Resin Microspheres for Neuroendocrine Tumor Liver Metastases

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ABSTRACT

Purpose: To evaluate long-term effects of yttrium-90 (^{90}Y) transarterial radioembolization (TARE) for unresectable hepatic metastases of neuroendocrine tumors (NETs).

Materials and Methods: Retrospective analysis of 93 patients (47 women, 46 men; mean age 59 y) who underwent resin-based ^{90}Y TARE was performed. Variables associated with overall survival were analyzed using univariate and multivariate models. Changes in serologic values and imaging characteristics were assessed with long-term follow-up.

Results: Unilobar TARE was performed in 48 patients, and staged bilobar TARE was performed in 45 patients. In multivariate analysis, ascites ($P = .002$) and extrahepatic metastases ($P = .038$) at baseline were associated with poor survival. Among 52 patients who had > 1 year of follow-up, significant increases in alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase were observed; however, only 4 patients experienced grade 3 serologic toxicities. Imaging signs of cirrhosis-like morphology and portal hypertension were observed in 15 of 52 patients, more frequently in patients treated with bilobar TARE compared with unilobar TARE. Patients treated with bilobar TARE exhibited significantly increased hepatobiliary enzymes and decreased platelet count. Sustained increases in liver enzymes were observed in patients with > 4 years of follow-up. No radioembolization-related liver failure or grade 4 toxicity was observed.

Conclusions: ^{90}Y radioembolization using resin microspheres demonstrated a high safety profile for NET liver metastases, with low-grade, although sustained, long-term liver toxicity evident > 4 years after treatment. Bilobar treatment suggested a trend for treatment-related portal hypertension. Ongoing research will help define parameters for optimizing durable safety and efficacy of radioembolization in this setting.

ABBREVIATIONS

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, HR = hazard ratio, NET = neuroendocrine tumor, TARE = transarterial radioembolization, ^{90}Y = yttrium-90

Neuroendocrine tumors (NETs) are relatively slow-growing neoplasms of neuroendocrine cell differentiation from a variety of origins (1). Although relatively rare, the incidence of NETs has increased over the past 3 decades with a prevalence of 35 per 100,000 patients (2). Of patients with NETs, 46%–93% have synchronous liver metastases at diagnosis (3), which is the most important prognostic factor affecting survival (4). Without treatment,

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5-year survival rate can be 20% in patients with NET liver metastases (5).

The management of NET liver metastases is clinically challenging. Surgical resection is preferred if > 90% of the disease can be safely removed. However, nearly 90% of patients present with multiple hepatic lesions not amenable to surgery (6). Alternative treatment options, such as thermal ablation (7,8), peptide receptor radionuclide therapy (9), external-beam radiation (10), systemic chemotherapy (11), and transarterial embolization and chemoembolization (12,13), have been explored for unresectable NET liver metastases.

Yttrium-90 (^{90}Y) transarterial radioembolization (TARE), also known as selective internal radiation therapy to distinguish it from external-beam radiation therapy, is an emerging treatment for unresectable NET liver metastases. TARE has been demonstrated to be safe and effective for treatment of NET liver metastases (14,15). The main advantages of TARE with ^{90}Y are its short half-life of 64 hours and low mean penetrance depth of 2–3 mm, which allows the radiation to be contained within the tumor bed with relative sparing of the surrounding parenchyma (16).

Data concerning long-term safety after ^{90}Y TARE are limited (17). Although previous retrospective reports have described biliary damage as a potential complication of therapy with ^{90}Y and chemoembolization, the potential long-term toxicity of ^{90}Y treatment is poorly understood. In many scenarios where radioembolization is performed in the salvage setting, long-term toxicity is not a major concern; however, because of the potential for longer survival in patients with NET liver metastases, the long-term toxicity of ^{90}Y therapy becomes more relevant. A previous report describing long-term hepatotoxicity in patients with NET liver metastases treated with ^{90}Y glass microspheres concluded that long-term hepatotoxicity solely attributable to ^{90}Y develops in a relatively small percentage of patients (18). The aim of the present study was to assess the prognostic factors and long-term (> 1 y after treatment) safety and toxicity of ^{90}Y TARE with resin microspheres for patients with NET liver metastases to further build on this experience.

MATERIALS AND METHODS

Study Population and Treatment Characteristics

With institutional review board approval, all patients with NET liver metastases treated with ^{90}Y TARE at a single institution between February 2007 and November 2015 were retrospectively reviewed. The following patients were included: (*a*) patients with NET liver metastases with available contrast-enhanced computed tomography (CT) or magnetic resonance (MR) imaging and who were not surgical candidates, (*b*) patients with available details of radiation treatment planning and delivery, and (*c*) patients 18–99 years old. Patients who had undergone prior treatment for NET liver metastases, including liver resection, systemic chemotherapy, transarterial embolization and chemoembolization, and locally ablative techniques were included. Exclusion criteria included (*a*) unsafe treatment owing to collateral arterial flow to the gastrointestinal tract, (*b*) hepatopulmonary shunt fraction > 20%, or (*c*) previous external-beam radiation therapy to the liver. All patients had baseline serologic values including liver function tests and complete blood count and contrast-enhanced CT or MR imaging before ^{90}Y treatment to assess the status of liver disease, tumor burden, signs of portal hypertension, and extrahepatic metastases.

Characteristics of the patients (n = 93) and treatments are shown in **Table 1**. Successful delivery of ^{90}Y was achieved in all patients. The mean age at the time of first treatment was 58.6 years ± 13.7 (range, 22–88 y) with a male-to-female ratio of 1:1. Eastern Cooperative Oncology Group performance status was 0 in 47 patients, 1 in 41 patients, and 2 in 5 patients. The primary tumor was classified as carcinoid tumor in 66 patients and islet cell tumor in 27 patients. Of the 71 patients whose tumor differentiation was known, 56 patients had well-differentiated tumors, and 15 had low-grade tumors. At baseline evaluation, 32 patients had extrahepatic metastases, and 16 patients had ascites. Child-Pugh class was A in 75 patients, B in 17 patients, and C in 1 patient. Previous treatments included transarterial embolization and chemoembolization in 24 patients, liver resection in 21 patients, systemic chemotherapy in 15 patients, and ablative therapy in 10 patients. No previous therapy was administered in 35 patients. The mean time interval from diagnosis of liver metastases to ^{90}Y treatment was 27 months (range, 1–216 months). The median follow-up duration was 15.0 months (interquartile range, 7.0–31.0 months). Of 93 patients, 23 patients were lost to follow-up, and 18 patients died, leaving 52 patients with > 1 year of clinical follow-up after initial TARE; 11 patients had > 4 years of follow-up. The mean total administered activity of ^{90}Y microspheres was 1.92 GBq ± 0.91. Unilobar TARE was performed in 48 patients, and staged sequential bilobar TARE (ie, right lobe followed by left lobe at a later date) was performed in 45 patients. For bilobar treatment, the time between the 2 treatments was usually 4–6 weeks. A total of 168 treatments were administered; 160 were lobar, and 8 were segmental. No single-session, whole-liver treatment was performed except in 3 patients who had undergone prior lobar resection. The mean number of TARE treatments was 1.8 (range, 1–4).

Preprocedural Work-up

Before treatment, patients underwent mapping visceral angiography. Collateral arteries supplying the gallbladder, stomach, or bowel were identified, and approximately 4 mCi of technetium-99m-labeled macroaggregated albumin was injected into the hepatic arteries in the anticipated location of the planned ^{90}Y delivery. Whole-body gamma scintigraphy, with or without combined single photon emission computed tomography/CT, was then performed to assess extrahepatic activity (eg, gastrointestinal flow) and to