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Neuroendocrine tumor liver metastases treated with yttrium-90 radioembolization

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ABSTRACT

Objective: Yttrium-90 (Y-90) radioembolization is an emerging treatment option for unresectable neuroendocrine liver metastases (NELM). However, the data regarding this treatment are currently limited. This study evaluates the efficacy and tolerability of Y-90 radioembolization and identifies prognostic factors for radiographic response and survival.

Methods and materials: Thirty-eight patients underwent Y-90 radioembolization for NELM at our institution between April 2004 and February 2012. Patients were assessed radiographically (RECIST criteria, enhancement), serologically, and clinically at 1 month, and then at every 3 months after treatment for tumor response, toxicity, and survival outcomes.

Results: Median length of follow-up was 17.0 months (IQR, 9.0–37.0). Median survival was 29.2 months. Three patients (9%) had a radiographic complete response to treatment, 6 (17%) had a partial response, 21 (60%) had stable disease, and 5 (14%) developed progressive disease. Two factors were significantly associated with a good radiographic response (complete/partial response): islet cell histological subtype ($p = 0.043$) and hepatic tumor burden ≥33% ($p = 0.031$). Multivariate analysis revealed that patients requiring multiple Y-90 treatments (HR 2.9, $p = 0.035$) and patients who had previously failed systemic therapy with octreotide/chemotherapy (HR 4.4, $p = 0.012$) had worse survival. Grade 3 serologic toxicity was observed in 2 patients (5%; hyperbilirubinemia, elevated alkaline phosphatase) after treatment. Grade 3 non-serologic toxicities included abdominal pain (11%), fatigue (11%), nausea/vomiting (5%), ascites (5%), dyspnea (3%), diarrhea (3%), and peripheral edema (3%). No grade 4 or 5 toxicity was reported.

Conclusions: Y-90 radioembolization is a promising treatment option for inoperable NELM and is associated with low rates of grade ≥ 3 toxicity.

1. Introduction

Neuroendocrine tumors (NETs) are a rare group of hormone-secreting tumors from which approximately 10% of all metastatic liver lesions are derived [1–3]. Between 25% to 93% of patients with NETs have synchronous neuroendocrine tumor liver metastases (NELM) at diagnosis [4–6], and these patients have a significantly worse symptomatic profile and prognosis [4,5,7,8].

Surgical resection is the only curative option for NELM. Unfortunately, nearly 90% of patients present with multiple hepatic lesions that render surgical cure impossible [9–12]. Alternative treatment options have been explored for unresectable NELM—systemic chemotherapy, [13–15] oral inhibitor of mammalian target of rapamycin [16,17], somatostatin analogues [18,19], and local ablation with cryotherapy or

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radiofrequency ablation [4,20–23]. However, these modalities are rarely curative and are typically only effective in patients with a few lesions <5 cm in diameter [24]. Intra-arterial strategies, including transcatheter arterial embolization/chemoembolization (TAE/TACE), and stereotactic body radiotherapy (SBRT) may lead to improved survival [25–32,33,34]. Peptide receptor radionuclide therapy, which involves an infusion of somatostatin analogues linked to radionuclides like Yttrium-90/Lutetium-177, has good response rate and survival [35].

Yttrium-90 (Y-90) radioembolization is an emerging treatment for unresectable liver tumors. Several studies have demonstrated the efficacy and safety of this technique for primary hepatocellular carcinoma and metastatic colorectal lesions [31,36]. A few studies have also initiated efforts toward evaluating the response of NELM to Y-90 microspheres. The purpose of this study is to critically assess the efficacy, prognostic factors, and toxicity associated with radioembolization using conventional Y-90 microspheres for the treatment of NELM in patients treated at a single institution.

2. Materials and methods

2.1. Patient population

With institutional review board approval, all patients with NELM treated with Y-90 radioembolization at Johns Hopkins Hospital between April 2004 and February 2012 were retrospectively reviewed. Prior to treatment with Y-90 radioembolization, treatment options were discussed in a multidisciplinary liver tumor board that includes physicians specializing in hepato-pancreatico-biliary surgery, interventional radiology, nuclear medicine, radiation oncology, and medical oncology. Y-90 radioembolization was reserved for patients with advanced (multifocal) disease within the liver not amenable to surgical resection and for those who progressed or had disease recurrence after resection. Y-90 treatment was not offered to patients with: (1) a total bilirubin level >3 mg/dL; (2) an albumin level <2.8 g/dL; (3) coagulopathy with a platelet count <50,000 and International Normalized Ratio >1.5; (4) any uncorrectable flow to the gastrointestinal tract observed on angiography; (5) a dose risk >30 Gy (0.61 GBq; 16.5 mCi) from a single treatment, an accumulated dose of 30 Gy to be delivered to the lungs based on a technetium Tc 99 macroaggregated albumin shunt scan, or a shunt study prediction of >20%; and/or (6) previous external beam radiation.

2.2. Treatment intervention

All patients on this study were treated with glass-based Y-90 microspheres (Therasphere®, Nordion Targeted Therapies, Ottawa, Ontario, Canada). Before radioembolization, percutaneous angiography with selective visceral catheterization was performed to evaluate the vascular anatomy and determine appropriate placement of the catheter tip for tumor location as well as embolization of relevant collateral arteries. To assess hepatopulmonary shunting and detect gastrointestinal deposition, 5–6 mCi of 99mTC-labeled macroaggregated albumin was injected into the hepatic artery. The shunt fraction was calculated by the ratio of lung to liver scintigraphic counts as detected on planar scintigraphy and corrected for the background activity. The ratios were then calculated as percentages. In the calculation for the estimated dose of Y-90 microspheres that would be shunted, the lungs were assumed to have a mass of 1 kg. The method of calculating the required TheraSphere (Nordion Targeted Therapies) activity for injection and the mean dose delivered to the liver and lungs has been published [37]. The activity required (Gbq) is the product of the target mean dose (Gy) and liver mass (kg) divided by 50 (Activity required (Gbq) = [desired dose (Gy)] × [target liver mass (kg)]/50). The liver volume in which the Y-90 microspheres were delivered (i.e., volume of distribution) was determined by CT or magnetic resonance imaging (MRI), and with the conversion factor of 1.03 g/cm^3, the lobar mass (kg) was determined. The shunt study preceded the treatment by at least 1 week to allow for dose calculations and delivery from the manufacturer. Access to the common femoral artery was obtained and selective hepatic arteriography was performed to delineate the blood supply feeding the liver tumors. The infusion setup was primed with 0.9% saline solution and connected to the infusion catheter. The Y-90 microspheres were injected in accordance with institutional radiation safety guidelines. Administration of the entire planned dose or reduced arterial flow (as opposed to occlusion of the vessel) were goals of the infusion. Patients were discharged the same day.

2.3. Follow-up and assessment of outcomes

Regular follow-up visits consisted of clinical assessment, a liver function test, and an MRI scan at 3–4 weeks after treatment, and every 3–6 months thereafter to assess for treatment response and late complications. Treatment response was assessed by comparing tumor dimensions on pre- and post-treatment MRI using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Accordingly, a complete response (CR) is defined as disappearance of lesions; partial response (PR) as a ≥ 30% decrease in the sum of the longest diameter of the index lesions; stable disease (SD) as a < 30% decrease or <20% increase in the sum of the longest diameter of the index lesions; and progressive disease (PD) as a ≥ 20% increase in the sum of the longest diameter of the index lesions or appearance of new lesions. Acute toxicity was assessed at 1, 3, and 6 months following Y-90 radioembolization therapy using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Table 1
Demographic and clinicopathologic characteristics for all patients (n = 38).

Characteristic	Value
Median age at treatment, years (range)	63 (45–80)
Sex	
Female	16 (42%)
Male	22 (58%)
ECOG performance status	
0	15 (39%)
≥1	23 (61%)
Extra-hepatic metastases	
Present	15 (39%)
Absent	23 (61%)
Location of primary	
Bowel	11 (29%)
Pancreas	14 (37%)
Other	9 (24%)
Unknown	4 (11%)
Histopathologic subtype	
Carcinoid	22 (58%)
Islet cell	14 (37%)
Tumor differentiation	
Well	17 (45%)
Moderate/Poor	6 (16%)
Unknown	15 (39%)
Previous therapy	
None	5 (13%)
Surgical resection	5 (13%)
Chemoembolization	8 (21%)
Ablation	5 (13%)
Chemotherapy	15 (39%)
Octreotide	16 (42%)
Hepatic tumor burden	
<33%	28 (74%)
33%–66%	6 (16%)
>66%	4 (11%)