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Radioembolization for Neuroendocrine Liver Metastases: Safety, Imaging and Long-term Outcomes

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Abstract

Purpose—To present long-term outcomes on the safety and efficacy of Yttrium-90 radioembolization in the treatment of unresectable hepatic neuroendocrine metastases refractory to standard-of-care therapy.

Methods and Materials—This study is Institutional Review Board approved and HIPPA compliant. 40 patients with hepatic neuroendocrine metastases were treated with ^{90}Y radioembolization at a single center. Toxicity was assessed using National Cancer Institute Common Terminology Criteria version 3.0. Response to therapy was assessed by size (WHO) and necrosis (EASL) guidelines. Time-to-response and overall survival was calculated using Kaplan-Meier method. Uni/multivariate analyses were performed.

Results—The median dose was 113 Gy (29 Gy-299 Gy). Clinical toxicities included fatigue (63%), nausea/vomiting (40%), abdominal pain (18%), fever (8%), diarrhea and weight loss (5%); grade 3 and 4 bilirubin toxicities were experienced in 2 and 1 patient(s), respectively. Different responses were noted by WHO (CR: 1.2%, PR: 62.7%) and EASL (CR: 20.5%, PR: 43.4%). Median time-to-response was 4 and 4.9 months by lesion and subject, respectively. 1, 2 and 3-year overall survival rates were 72.5%, 62.5% and 45%, respectively. ECOG performance score 0 ($p<0.0001$), tumor burden ≤25% ($p=0.0019$), albumin ≥3.5 g/dL ($p=0.017$) and bilirubin ≤1.2 mg/dL ($p=0.002$) prognosticated survival on univariate analysis; only ECOG performance score 0 and bilirubin ≤1.2 mg/dL prognosticated better survival outcome on multivariate analysis ($p=0.0001$ and $p=0.02$).

Conclusion—^{90}Y therapy for hepatic neuroendocrine metastases leads to satisfactory tumor response and patient survival with low toxicity in line with published national guidelines

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recommending radioembolization as a potential option for unresectable hepatic neuroendocrine metastases.

Keywords

radioembolization; neuroendocrine metastasis; safety; response; survival

INTRODUCTION

Neuroendocrine tumors are a group of uncommon tumors; their overall age adjusted incidence rates vary from 2-3 cases per 100,000.(1) They typically arise in the endocrine cells and glands located throughout the body; the most common sites being gastrointestinal tract and lungs. The most common types are carcinoids, pancreatic islet cell tumors, paragangliomas, pheochromocytomas and medullary thyroid cancers. Given the diverse biologic behavior of these tumors, some patients may remain asymptomatic for years; others may develop symptoms due to tumor bulk or hormonal hypersecretion (carcinoid syndrome: excessive serotonin release leading to flushing, wheezing, diarrhea and right sided valvular heart disease).(1) 50-95% of patients with mNETs develop liver metastases; 80% with advanced liver disease may die within 5 years of diagnosis.(2)

Chemotherapy has been effective in metastatic islet cell tumors with response rates of up to 60%; response rates are lower in patients with carcinoid (20%).(3) Recently, two large scale randomized placebo controlled studies have shown better progression-free survival and response outcomes in patients with advanced neuroendocrine tumors treated with biological therapies (sunitinib, everolimus) when compared to groups of patients treated with placebos.(4, 5) There is history of successful treatment of such tumors with external beam radiotherapy; however, the diffuse nature of hepatic metastatic disease makes the use of external irradiation less applicable and difficult.(2) Historically, treatment options for liver metastases from neuroendocrine tumors have centered on surgical resection with the intent of removing entire tumor, debulking, or elimination of carcinoid syndrome when present; these have resulted in a 5-year survival rate of 60-80%; however, resection is often limited by location or extent of metastases.(6) Liver transplantation has been attempted with mixed results with 5-year survival rates reported between 36 & 47%.(7)

Since hepatic metastases from neuroendocrine tumors contribute significantly to the morbidity and mortality, liver-directed therapies are considered for those with unresectable lesions. These include thermal ablation, cryotherapy, bland or chemoembolization. Chemoembolization has resulted in encouraging response rates and survival outcomes.(8) Studies suggest that outcomes are similar in patients managed by chemo- or bland hepatic artery embolization.(9)

More recently, radioembolization has been recognized by the National Comprehensive Cancer Networks as a treatment option for mNETs.(1) Although published data are limited, results based on ^{90}Y therapy show encouraging safety profiles, response rates and survival outcomes. In this report, we describe long-term outcomes in a 40-patient cohort treated with ^{90}Y for mNETs refractory to systemic therapy with imaging-confirmed progression.

METHODS

Patient Cohort

Forty patients with liver dominant mNETs were enrolled in this study between 2003 and 2007. The study was approved by Institutional Review Board and is HIPPA compliant. All patients provided written informed consent for treatment. This study represents a

retrospective review of prospectively collected data. Study inclusion criteria included: 1) unresectable mNETs refractory to systemic treatment as determined by oncology and interventional radiology with imaging-confirmed progressive disease; 2) ECOG performance score ≤2; 3) ability to undergo angiography and selective visceral catheterization; and 4) adequate hematologic parameters (granulocyte count $\geq 1.5 \times 10^9$ /L, platelets $\geq 50 \times 10^9$ /L), renal function (creatinine ≤2.0 mg/dL) and liver function (bilirubin ≤2.0 mg/dL). Unresectability was determined by assessing factors such as tumor distribution/size, extrahepatic metastases, liver function tests and medical comorbidities at weekly gastrointestinal tumor board. Exclusion criteria included: 1) significant extrahepatic disease; 2) evidence of uncorrectable gastrointestinal flow observed on angiography or ^{99m}Tc-MAA scans; 3) the possibility of estimated lung dose to be >30 gray (Gy) in a single session; and 4) concurrent chemotherapy or radiotherapy. In patients taking octreotide, this agent was not stopped for ^{90}Y therapy.

Patient Evaluation and Workup

All patients underwent history and physical examinations with baseline laboratory tests and radiological imaging. A pretreatment angiogram was performed to determine proper catheter position and identify any collateral flow to the gastrointestinal tract.(10) Prophylactic embolization of aberrant vessels was performed when appropriate. ^{99m}Tc-MAA scanning was performed to detect any unobserved GI flow and to estimate the lung shunt fraction.

Treatment Plan

Yttrium-90 device (TheraSphere®, MDS Nordion, Canada) is currently approved for patients with unresectable HCC.(11) It consists of 20-30 micron-sized nonbiodegradable microspheres in which Yttrium is the integral constituent. ^{90}Y is a pure beta emitter with a physical half-life of 64.1 hours. The method of calculating the required activity for injection and the actual dose delivered to the liver has been published previously.(12, 13) All patients received ^{90}Y therapy via a lobar arterial approach.

All procedures were performed on outpatient basis. Prophylactic octreotide (200 ug subcutaneous) was administered to all patients immediately before radioembolization. A 2-week course of proton pump inhibitors was prescribed following treatment.

Data Collection and clinical follow up

All patients were evaluated by history, physical exam, laboratory values and radiological imaging at four weeks post treatment and then every 2-3 months. All data were collected prospectively. Although the last patient was enrolled in 2007, we closed the data on December 25, 2010 in order to report mature survival outcomes. Patients were followed until death; final date of death was confirmed by using the social security death index and/or direct confirmation by family members. Otherwise, patients were censored at the last known clinic follow-up.

Toxicity analysis

Clinical and laboratory adverse events were recorded using National Cancer Institute Common Terminology Criteria v3.0 during routine clinic visits. Adverse events were assessed one month after treatment, and then every 2-3 months coinciding with imaging follow-up. Grade 3-4 laboratory and all clinical toxicities were reported at any time following treatment (no 30-day time cut-off). In order to report conservatively, these are reported herein without any attribution of causality.

Response analysis

Tumor response was assessed by using WHO (size) criteria and EASL (necrosis) guidelines per previously published methodology.(14-17) CT or MRI was used for assessing radiological response. Imaging modality (CT/MRI) remained consistent for all patients. A total of 83 lesions (mean: 2.1 lesions/patient) were identified as target/index lesions for imaging response and follow-up.(16) Time-to-response was calculated using Kaplan-Meier method. Time to WHO response was defined as the time from first treatment to a decrease of at least 50%.

Overall Survival, Univariate and Multivariate Analyses

All 40 patients were available to calculate overall survival (Kaplan-Meier) and the effect of different covariates on survival. Univariate (Kaplan-Meier) and multivariate analyses (Cox proportional hazards) were conducted to compare survival between groups. In order to interpret the data most conservatively, p-values <0.05 on univariate analyses were corrected for multiple comparisons using Bonferroni methodology.(18) Factors were included in the multivariate model if p<.25 in univariate analysis (unadjusted for multiple comparisons).

RESULTS

Baseline Characteristics

Table 1 summarizes the baseline characteristics. Most subjects were <65 years old (68%) with ECOG performance score 0 (75%) and exhibited multifocal (100%) bilobar (95%) disease with <25% tumor burden (80%). 65% of patients had liver-only disease. Site of primary neuroendocrine tumor was unknown in most cases (35%); for cases where it was known, small intestine and pancreas constituted the most common primary sites (25% and 22.5%, respectively). 78% had received previous systemic therapy (i.e. octreotide, interferon, streptozotocin). The majority (68%) had received no previous liver-directed therapy.

Treatment

40 patients underwent a total of 99 treatment sessions (median 2.0, range 1-3 per patient). 14 (35%) patients did not require any prophylactic embolization. Median activity infused and ultimately delivered to tissue corrected for decay was 1.98 GBq. Median radiation dose per treatment site (liver) and lungs was 113 Gy and 3.81 Gy, respectively (Table 2).

Toxicities

Table 3 summarizes the treatment toxicities. Clinical toxicities included fatigue in 25 (63%), abdominal pain in 7 (18%), nausea and vomiting in 16 (40%), fever and chills in 3 (8%) and, diarrhea and weight loss in 2 (5%) patients. Among laboratory toxicities, two patients experienced grade 3 bilirubin toxicity (one of these occurred at 8 months, the other developed in a patient with a previous Whipple procedure). One patient experienced grade 4 bilirubin toxicity. 15 (38%) experienced grade 3 lymphocyte toxicity. Grade 3 albumin, AST, and ALP toxicities were experienced in 1, 1 and 2 patients, respectively. One patient experienced radiation cholecystitis requiring cholecystectomy. No patient experienced GI ulceration and there were no treatment-related deaths.

Radiologic Response

Table 4 presents the response analysis. Eighty three lesions were used to assess response to therapy by WHO criteria and EASL guidelines. By WHO criteria, complete response was noted in 1 (1.2%) lesion, partial response in 52 (62.7%) lesions, stable disease in 27 (32.5%) lesions and progression in 3 (3.6%) lesions. By lesion size, response rate recorded was 41%

in lesions ≤9 cm^2, 18% in lesions between 9 & 36 cm^2 and 5% in lesions ≥36 cm^2. Of all lesions, 94% showed at least some decrease in size, whereas 64% of lesions showed greater than 50% reduction in size. Median time to response (WHO) was 4 months by lesion and 4.9 months by subject. By EASL guidelines, 17 (20.5%) lesions showed 100% necrosis and 36 (43.4%) lesions showed partial response.

Symptomatic Response

Of 25 patients symptomatic at baseline, 21 reported subjective improvement following treatment. Four out of 25 patients continued to exhibit symptoms after ^{90}Y therapy.

Survival

Survival outcomes are summarized in Table 4. The mean and median follow-up times were 31 and 27 months, respectively. 26 patients had died at the time of this analysis. Median overall survival time was 34.4 months (range 1.1 to 75.5 months). 1, 2 and 3-year survival rates for all patients were 72.5%, 62.5% and 45% from ^{90}Y treatment.

Uni/multivariate analyses are summarized in Table 5. Univariate analysis revealed that ECOG performance score 0 ($p<0.0001$), tumor burden ≤25% ($p=0.0019$), albumin ≥3.5 g/dL ($p=0.017$) and bilirubin ≤1.2 mg/dL ($p=0.002$) favorably prognosticated survival; however, only ECOG performance score 0, tumor burden ≤25% and bilirubin ≤1.2 mg/dL remained significant even after correction for multiple comparisons by Bonferroni methodology.(18) Absence of extrahepatic disease trended towards trended toward prognostication of better survival ($p=0.108$). Interestingly, the number of lesions did not appear to affect survival outcome. On multivariate analysis, only ECOG performance score 0 and bilirubin ≤1.2 mg/dL independently prognosticated better survival ($p=0.0001$ and $p=0.02$, respectively).

DISCUSSION

Neuroendocrine tumors are a group of indolent tumors that grow slowly but frequently metastasize to the liver.(19) Surgical options have remained the cornerstone of therapy for hepatic neuroendocrine metastases. However, it has been difficult to determine in phase II trials if therapy results in any improvement in disease control and survival outcomes given the indolent nature of the disease.(20) Despite being indolent, they can cause significant morbidity and mortality due to liver metastases. Therefore, it is of particular interest to study liver-directed therapies for neuroendocrine metastases for reducing tumor burden, improving survival and minimizing symptoms due to hormonal hypersecretion. ^{90}Y radioembolization is rapidly establishing its role as palliative therapy in the treatment of HCC.(14) Treatment with ^{90}Y is often not limited by lesional characteristics and patient comorbidities and therefore offers a potential option for those who cannot be treated by surgical resection. Studies have shown that a majority patients treated with ^{90}Y for hepatic neuroendocrine metastases have shown partial response on imaging follow up.(2, 21, 22)

^{90}Y is administered via a trans-arterial catheter into the hepatic artery perfusing the tumors. Hepatic primary and secondary tumors are hypervascular, deriving their supply from the hepatic artery, whereas the normal hepatic parenchyma is supplied by portal vein.(23) Thus, the high radiation toxic effect of ^{90}Y is directed towards the tumor cells and the normal parenchyma is relatively spared. Although the treatment algorithm for radioembolization is based on that for chemoembolization, there are distinct differences in the mechanism of action. Following accepted standards for ^{90}Y administration should minimize the incidence of adverse effects.(24)

The data presented in this report of our study support the notion of ^{90}Y being a safe and efficacious therapy in mNETs. Most of the clinical toxicities were transient and controlled

symptomatically without requiring hospitalization. The grade III and IV laboratory toxicities were limited in number and are reported herein if experienced any time after treatment. These toxicities compare favorably with those observed in other cohort studies of ^{90}Y.(2, 17) The inadvertent spread of microspheres can lead to serious GI toxicities; these can be mitigated by prophylactic coil embolization. In our cohort, 26 of 40 patients received coil embolization. No treatment-related gastric ulcer was encountered in our cohort. In addition, none of the patients experienced radiation pneumonitis. However, there was one case of radiation cholecystitis requiring cholecystectomy.

The highly localized radiation effect translated into a satisfactory response rate. Of all lesions, 94% showed at least some decrease in size and 64% showed greater than 50% reduction (WHO response criteria). In this regard, these results are comparable to those of recent studies.(2, 22) Survival outcomes were found to be encouraging. The 1-year survival rate was 72.5% for all subjects. Univariate analysis revealed that ECOG performance score 0, liver replacement by tumor <25%, normal baseline bilirubin and albumin levels had favorable prognostic effects on survival. Lack of extrahepatic disease also favored better survival outcomes.

Liver-directed locoregional therapies have gained widespread acceptance for the treatment of mNETs. Several studies have demonstrated encouraging results with ^{90}Y radioembolization. In a multi-institutional study with 42 patients treated with ^{90}Y, Rhee et al concluded that median overall survival was 22-28 months, with >90% disease control.(21) In another retrospective multi-institutional study (largest to date), Kennedy et al investigated ^{90}Y microsphere treatment in 148 patients. They reported no acute or delayed grade III adverse events in 67% of patients; median survival time was 70 months with a partial response rate of 60.5%.(2) Furthermore, Saxena et al reported a median overall survival of 35 months; complete and partial response was observed in 15% and 40% patients, respectively. They also demonstrated that response to therapy, low hepatic tumor burden, well-differentiated tumor and absence of extrahepatic disease predicted improved survival.(22) In another study, King et al reported complete and partial response rate at 18 and 32%, respectively, in a 34 patient cohort; and mean survival time was 29.4 months.(25) A recent study in hepatocellular carcinoma has suggested that response may also serve as a prognosticator of overall median survival.(26) These studies demonstrate the reproducible outcomes in terms of response rates, toxicity profiles and long-term outcomes in mNETs.

Chemoembolization arguably is the worldwide arterial standard of care for mNETs. Recently, Dong et al investigated chemoembolization in a series of 123 patients, concluding that 62% of patients achieved partial response. Overall survival rates were 59%, 36% and 20% at 3, 5 and 10 years, respectively.(8) De Baere et al investigated the use of doxorubicin-eluting beads in a 20 patient cohort. Partial response, stable and progressive disease were noted in 16, 3 and 1 patients, respectively. At 15 months follow-up, 9 patients maintained stable disease, with 10 exhibiting progressive disease. They concluded that TACE with drug-eluting beads is well-tolerated and appears effective.(27) In another retrospective 48 patient study, Vogl et al investigated chemoembolization with mitomycin C alone or in combination with gemcitabine in patients with mNETs. They observed no major complications; response rate varied between 11.1% and 23.3%; 5-year survival varied between 11.11% & 46.67%. They concluded that transarterial hepatic chemotherapy using mitomycin C and gemcitabine can be an effective therapeutic protocol for mNETs.(28)

The role of bland embolization in hepatic neuroendocrine metastases also requires consideration. In an 84 patient study, Strosberg et al observed a 36 month median overall survival time; radiologic response was observed in 11 of 23 patients. They concluded that hepatic artery embolization results in clinical and radiographic responses that often lead to

regression in patients with unresectable metastases from neuroendocrine tumors.(29) In another study with 23 patients, Loewe et al demonstrated a median survival time of 69 months.(30) Eriksson et al investigated bland embolization in a series of 41 patients, reporting a median survival time of 80 months; tumor response was 50%.(31) Survival from time of treatment or initial diagnosis likely explains the differences in overall survival times.

The various studies discussed above are summarized in Table 6. For comparison, the results of our study are also summarized, showing that the toxicity profile, response rate and survival time in our study are all comparable to observations of investigators at other centers. These studies again demonstrate that locoregional therapies have gained widespread adoption and that outcomes are comparable between centers. This is encouraging given the few patients that may benefit from curative treatments in this condition.

CONCLUSION

^{90}Y radioembolization for mNETs is a safe and effective therapy that produces tumor responses in the majority of patients and yields promising survival outcomes. This structured cohort analysis was able to provide the necessary scientific background and rationale for our next analysis, thereby permitting hypothesis generation and accurate statistical powering of ongoing clinical trials. Future studies should compare ^{90}Y to other systemic and locoregional therapies.

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References

1. Clark OH, Benson AB 3rd, Berlin JD, et al. NCCN Clinical Practice Guidelines in Oncology: neuroendocrine tumors. J Natl Compr Canc Netw. 2009; 7:712–747. [PubMed: 19635226]
2. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol. 2008; 31:271–279. [PubMed: 18525307]
3. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med. 1992; 326:519–523. [PubMed: 1310159]
4. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011; 364:501–513. [PubMed: 21306237]
5. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011; 364:514–523. [PubMed: 21306238]
6. Norton JA. Surgical treatment of neuroendocrine metastases. Best Pract Res Clin Gastroenterol. 2005; 19:577–583. [PubMed: 16183528]
7. Florman S, Toure B, Kim L, et al. Liver transplantation for neuroendocrine tumors. J Gastrointest Surg. 2004; 8:208–212. [PubMed: 15036197]
8. Dong XD, Carr BI. Hepatic artery chemoembolization for the treatment of liver metastases from neuroendocrine tumors: a long-term follow-up in 123 patients. Med Oncol. 2010
9. Ruutiainen AT, Soulen MC, Tuite CM, et al. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. J Vasc Interv Radiol. 2007; 18:847–855. [PubMed: 17609443]
10. Lewandowski RJ, Sato KT, Atassi B, et al. Radioembolization with (90)y microspheres: angiographic and technical considerations. Cardiovasc Intervent Radiol. 2007; 30:571–592. [PubMed: 17516113]
11. Salem R, Thurston KG, Carr BI, et al. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. J Vasc Interv Radiol. 2002; 13:S223–229. [PubMed: 12354840]

12. Salem R, Thurston KG. Radioembolization with 90Yttrium Microspheres: A State-of-the-Art Brachytherapy Treatment for Primary and Secondary Liver Malignancies: Part 1: Technical and Methodologic Considerations. J Vasc Interv Radiol. 2006; 17:1251–1278. [PubMed: 16923973]
13. Salem R, Lewandowski RJ, Gates VL, et al. Research reporting standards for radioembolization of hepatic malignancies. J Vasc Interv Radiol. 2011; 22:265–278. [PubMed: 21353979]
14. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization Results in Longer Time-to-Progression and Reduced Toxicity Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2011; 140:497–507. e492. [PubMed: 21044630]
15. Riaz A, Memon K, Miller FH, et al. Role of the EASL, RECIST, and WHO response guidelines alone or in combination for hepatocellular carcinoma: Radiologic–pathologic correlation. Journal of Hepatology. 2011; 54:695–704. [PubMed: 21147504]
16. Riaz A, Miller FH, Kulik LM, et al. Imaging response in the primary index lesion and clinical outcomes following transarterial locoregional therapy for hepatocellular carcinoma. JAMA. 2010; 303:1062–1069. [PubMed: 20233824]
17. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010; 138:52–64. [PubMed: 19766639]
18. Gyorffy B, Gyorffy A, Tulassay Z. The problem of multiple testing and solutions for genome-wide studies. Orv Hetil. 2005; 146:559–563. [PubMed: 15853065]
19. Shebani KO, Souba WW, Finkelstein DM, et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. Ann Surg. 1999; 229:815–821. discussion 822-813. [PubMed: 10363895]
20. Kulke MH. Gastrointestinal neuroendocrine tumors: a role for targeted therapies? Endocr Relat Cancer. 2007; 14:207–219. [PubMed: 17639038]
21. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. Ann Surg. 2008; 247:1029–1035. [PubMed: 18520231]
22. Saxena A, Chua TC, Bester L, et al. Factors predicting response and survival after yttrium-90 radioembolization of unresectable neuroendocrine tumor liver metastases: a critical appraisal of 48 cases. Ann Surg. 2010; 251:910–916. [PubMed: 20395859]
23. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954; 30:969–977. [PubMed: 13197542]
24. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007; 68:13–23. [PubMed: 17448867]
25. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer. 2008; 113:921–929. [PubMed: 18618495]
26. Memon K, Kulik L, Lewandowski RJ, et al. Radiographic Response to Locoregional Therapy in Hepatocellular Carcinoma Predicts Patient Survival Times. Gastroenterology. 2011
27. de Baere T, Deschamps F, Teriitheau C, et al. Transarterial chemoembolization of liver metastases from well differentiated gastroenteropancreatic endocrine tumors with doxorubicin-eluting beads: preliminary results. J Vasc Interv Radiol. 2008; 19:855–861. [PubMed: 18503899]
28. Vogl TJ, Gruber T, Naguib NN, et al. Liver metastases of neuroendocrine tumors: treatment with hepatic transarterial chemotherapy using two therapeutic protocols. AJR Am J Roentgenol. 2009; 193:941–947. [PubMed: 19770314]
29. Strosberg JR, Choi J, Cantor AB, et al. Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors. Cancer Control. 2006; 13:72–78. [PubMed: 16508629]
30. Loewe C, Schindl M, Cejna M, et al. Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and lipiodol: assessment of mid- and long-term results. AJR Am J Roentgenol. 2003; 180:1379–1384. [PubMed: 12704055]

31. Eriksson BK, Larsson EG, Skogseid BM, et al. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. Cancer. 1998; 83:2293–2301. [PubMed: 9840528]

Abbreviations

ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
CI	Confidence interval
CT	Computerized tomography
DEB	Drug-eluting beads
ECOG	Eastern Cooperative Oncology Group
EASL	European Association for the Study of the Liver disease
GBq	Gigabecquerel
Gy	Gray
HCC	Hepatocellular carcinoma
HIPPA	Health Insurance Portability and Accountability Act
MRI	Magnetic Resonance Imaging
mNET	Metastatic Neuroendocrine Tumors
NCCN	National Comprehensive Cancer Network
NET	Neuroendocrine Tumor
TACE	Transarterial Chemoembolization
^{99m}Tc-MAA	Technetium labeled Macroaggregated Albumin
WHO	World Health Organization

Table 1

Baseline Characteristics

Characteristic		N (%)
Age (years)	<65	27 (68)
	≥65	13 (32)
Ethnic group	Caucasian	36 (90)
	African-American	4 (10)
Gender	Male	22 (55)
	Female	18 (45)
Histology	Carcinoid	35 (87.5)
	Islet cell	2 (5)
	Gastrinoma	1 (2.5)
	Pheochromocytoma	1 (2.5)
	Atypical	1 (2.5)
Location of Primary	Small intestine	10 (25)
	Pancreas	9 (22.5)
	Kidney	3 (7.5)
	Stomach	2 (5)
	Adrenal	1 (2.5)
	Lung	1 (2.5)
	Unknown	14 (35)
Symptoms of carcinoid syndrome	Yes (N=25) *	Diarrhea: 16 (64%)
		Flushing: 14 (56%)
		Abdominal pain: 8 (32%)
		Weight loss: 5 (20%)
		Palpitations, Sweating, Wheezing: 2 (8%)
Tumor burden	≤25%	32 (80)
	26%-50%	6 (15)
	>50%	2 (5)
Lobes affected	Unilobar	2 (5)
	Bilobar	38 (95)
Distribution	Solitary	0 (0)
	Multifocal	40 (100)
Portal vein invasion	Absent	39 (98)
	Present	1 (2)
Extrahepatic metastases	Absent	26 (65)
	Present (peritoneal, lymph nodes)	14 (35)
ECOG Performance Score	0	30 (75)
	1	9 (23)
	2	1 (2)

Characteristic		N (%)
Previous systemic therapy	Octreotide	28 (70)
	Other (i.e. interferon, streptozotocin)	3 (8)
	None	9 (22)
Previous Liver-directed therapy	None	27 (68)
	TACE	5 (13)
	RFA	2 (5)
	Resection	3 (7)
	RFA + Resection	2 (5)
	Other (Bland)	1 (2)

Abbreviation: ECOG, Eastern Cooperative Oncology Group; RFA, Radiofrequency ablation; TACE, Trans-arterial Chemoembolization,

* patients may exhibit 1 or more symptoms

Table 2

Treatment Characteristics

Treatment Characteristic	Per treatment session	
	Mean (95% CI)	Median (range)
Activity at infusion (corrected for decay)	2.14 GBq (1.9, 2.4)	1.98 GBq (0.18, 5.02)
Radiation dose to treatment site	115 Gy (106.6, 122.9)	113 Gy (29, 298.7)
Radiation dose to lungs	5.4 Gy (4.2, 6.6)	3.8 Gy (0.21, 26.7)

Abbreviations: CI: Confidence interval; GBq: Gigabecquerel; Gy: Gray;

Table 3

Clinical and Biochemical Toxicities

Adverse Event	No. of Patients	Percentage
All Clinical Toxicities		
Fatigue	25	63
Abdominal Pain	7	18
Nausea/Vomiting	16	40
Fever/ Chills	3	8
Diarrhea	2	5
Weight loss	2	5
Radiation Cholecystitis	1	2
Grade 3 and 4 Laboratory Toxicities		
Hyperbilirubinemia	3	8
Hypoalbuminemia	1	2
Elevated serum Aspartate Aminotransferase level	1	2
Elevated serum Alkaline Phosphatase level	2	5
Lymphopenia	15	38

Table 4

Survival and Response

Overall Survival (N=40)			
Median Survival in months (Range)	**1-year [N (%)]**	**2-year [N (%)]**	**3-year [N (%)]**
34.4 (1.1 - 75.5)	29 (72.5)	25 (62.5)	18 (45)

WHO Response			
Response State	N (%)	Time to Response (By lesion)	Time to Response (By subject)
CR	1 (1.2)	4 mo (range 2.6-5.4)	4.9 mo (range 1.8-5.4)
PR	52 (62.7)		
SD	27(32.5)		
PD	3 (3.6)		

EASL Response		
Response State	By lesion (N=83)	By subject
50-99% necrosis	36 (43.4)	25 (71.4)
100% necrosis	17 (20.5)	10 (28.6)

Abbreviations: EASL, European Association for the Study of the Liver disease; WHO, World Health Organization; CR, Complete Response; PR, Partial Response; SD; Stable Disease; PD, Progressive Disease

Table 5

Uni/ Multivariate analysis

Univariate analysis (Survival)							Multivariate analysis (Cox Proportional Hazards Model)**	
Variable	**Category**	**N**	**Median Survival in months (Range)**	**Hazard Ratio (CI)**	**p value**	**Adjusted p* value**	**CI**	**P value**
Gender	Female	18	37.9 (3.5 - 59.2)	0.66 (0.31- 1.42)	0.281			
	Male	22	26.4 (1.1 - 72.9)	1				
Age	<65	27	39.1 (1.1 – 72.9)	0.48 (0.20 – 1.15)	0.058		0.41 (0.16 – 1.05)	0.066
	≥65	13	22.4 (1.7 - 59.2)	1				
ECOG Performance score	0	30	56.2 (3.5 - 72.9)	0.13 (0.03 – 0.55)	**<0.0001**	**0.008**	0.04 (0.009 – 0.19)	**0.0001**
	>0	10	6.9 (1.1 - 10.6)	1				
Liver replacement by tumor %	≤ 25%	32	56.1 (1.1 - 72.9)	0.29 (0.09 – 0.98)	**0.0019**	**0.015**	0.63 (0.20 – 1.91)	0.41
	> 25%	8	15.4 (1.7 – 34.4)	1				
Lesions >4	No	3	37.9 (4 - 37.9)	0.79 (0.16 – 3.91)	0.755			
	Yes	37	29.9 (1.1 - 72.9)	1				
Extrahepatic disease	No	26	39.1 (1.1 - 72.9)	0.53 (0.22 - 1.29)	0.108		0.73 (0.25 – (2.06)	0.55
	Yes	14	22.1 (3.5 - 56.2)	1				
Albumin	≥3.5 g/dL	15	58.9 (1.7 – 72.9)	0.39 (0.18 – 0.84)	**0.017**	0.08	0.45 (0.15 – 1.34)	0.15
	<3.5 g/dL	25	22.0 (1.1 – 56.1)	1				
Bilirubin	≤1.2 mg/dL	38	37.9 (1.1 – 72.9)	0.14 (0.004 – 5.02)	**0.002**	**0.016**	0.08 (0.01-0.74)	**0.02**
	>1.2 mg/dL	2	5.2 (1.7 – 8.7)	1				

*Adjusted for multiple comparison (correction factor=8)

**Factors were included in multivariate analysis if p <.25 in univariate analysis (unadjusted for multiple comparisons)

Abbreviations: ECOG: Eastern Cooperative Oncology Group

Table 6

Outcomes comparison to other studies

Study	No. of patients	Device/Method used	Toxicity	Radiologic Response	Survival times & rates
Rhee[23]	42	**Yttrium-90 (glass)**	Grade III/IV (14%)	54%	Median:22 months
		Yttrium-90 (resin)		50%	Median: 28 months
Kennedy[2]	148	**Yttrium-90**	33% (grade III), fatigue (6.5%)	63%	Median: 70 months
King[25]	58	**Yttrium-90**	Radiation gastritis (2 patients), duodenal ulcer (1 patient),	39%	Median : 36 months 1,2,3 year survival: 86%, 58%, and 47%
Saxena[24]	48	**Yttrium-90**	0.5% (grade III) 1 patient (biliary obstruction)	54%	Median: 35 months 1,2,3 year survival: 87%, 62%, and 42%
Dong[8]	123	**TACE**	Abdominal pain (44%), diarrhea (30%), weight loss (22%)	62%	Mean: 3.3 years 3, 5 and 10 year survival : 59%, 36% and 20%
de Baere[26]	20	**TACE with doxorubicin eluting beads**	Nausea (61%), fever (36%)	80%	-
Vogl[27]	48	**TACE with mitomycin C**	Nausea and vomiting (27.8%), abdominal pain (11.1%)	11.1%	Median:38.6 7 months 5 year: 11.11%
		TACE with mitomycin C + gemcitabine	Nausea and vomiting (16.7%), abdominal pain (10%)	23.33%	Median: 57.1 5 year: 46.67%
Loewe[29]	23	**Bland embolization**	-	73%	Median: 69 months 1 and 5 year survival: 95.7% and 65.4%
Eriksson[30]	41	**Bland Embolization**	Postembolization syndrome (all), nausea (33%), fever (7 patients), median hospitalization: 12 days	50%	Median: 80 months 5 year: 60%
Current Study	40	**Yttrium-90**	Fatigue (63%, all grades), nausea/vomiting (40%, all grades), grade III, IV (bilirubin:8%; albumin:2%; lymphocute:38%)	WHO:64%; EASL: 63.9%	Median: 34.4 months 1,2, 3 year survival: 72.5%, 62.5%, 45%

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