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Outcomes After Transarterial Embolization of Neuroendocrine Tumor Liver Metastases Using Spherical Particles of Different Sizes

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Abstract

Purpose To evaluate initial response and overall survival of neuroendocrine tumor (NET) liver metastases initially treated with transarterial embolization (TAE) using spherical particles of different sizes.

Methods A single-institution retrospective review was performed of 160 patients with NET liver metastases initially treated with TAE using < 100 µm ($n = 77$) or only ≥ 100 µm ($n = 83$) spherical particles. For each patient, we evaluated: initial response by mRECIST, time to progression, overall survival, complications, primary site, tumor grade and degree of differentiation, volume of liver disease, extrahepatic disease, NET-related symptoms, comorbidities, Child–Pugh score, performance status, lobar versus selective embolization, and arteriovenous shunting.

Results Initial response was higher for TAE using particles < 100 versus TAE using only particles ≥ 100 µm (64 vs 42%, $p = 0.007$). Multivariate logistic regression showed that use of particles < 100 µm and liver $< 50\%$ replaced with tumor were independent predictors of a better initial response rate. There was no difference in major or minor complications between the two particle size groups. Median overall survival after TAE was 55 months for well- to moderately differentiated NET and 13 months for poorly differentiated or undifferentiated NET. There was no significant difference in survival between TAE patients treated with < 100 versus only ≥ 100-µm particles.

Conclusion NET patients treated with TAE using particles < 100 µm had better initial response, but the same overall survival, compared to TAE using only particles ≥ 100 µm.

Keywords Neuroendocrine tumor · Carcinoid · Transarterial embolization · Particle size

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Introduction

The best initial locoregional therapy for neuroendocrine tumor (NET) liver metastases is unknown. National Comprehensive Cancer Network (NCCN) guidelines recommend either transarterial embolization (TAE), transarterial chemoembolization (TACE), or radioembolization (RE)

for progressive unresectable liver-dominant NET metastases that are either symptomatic or have a large tumor burden [1].

Prior studies have shown mixed results when comparing TAE, TACE, and RE. In a retrospective study, patients with NET liver metastases treated with TAE or TACE had no difference in survival, but patients treated with radioembolization had worse survival [2]. However, a meta-analysis showed similar survival after TACE and radioembolization [3]. Radioembolization of NET is associated with long-term liver toxicity [4]. TACE using drug-eluting beads is associated with a high rate of biliary complications [5].

To our knowledge, there is no published human data comparing outcomes after TAE using different particle sizes. In rabbits, TAE of liver tumors (VX2) using 300–500-μm Embospheres resulted in particles depositing outside the tumor, while 100–300-μm Embospheres deposited inside the tumor [6]. However, even 100–300-μm particles failed to generate hypoxia in rabbit VX2 tumors [7]. This could be due to the development of microcollaterals after embolization [8], allowing continued perfusion of the tumors. Particles smaller than 100 μm might be required to occlude end arterioles, in order to achieve tumor ischemia and necrosis. For both hepatocellular carcinoma [9] and NET [2], outcomes after TAE and TACE are similar, suggesting that ischemia is the dominant mechanism causing tumor necrosis.

The purpose of this study was to evaluate initial response, complications, time to progression, and overall survival (OS) of neuroendocrine tumor (NET) liver metastases initially treated with TAE using spherical particles of different sizes (< 100 vs ≥ 100 μm). In addition, this study examined factors that predict outcomes after TAE.

Methods

Patient Selection

This Health Insurance Portability and Accountability Act (HIPAA)-compliant retrospective study was approved by the Institutional Review Board (IRB). All liver tumor embolization procedures performed from June 2009 to April 2016 were reviewed: 1278 procedures on 671 patients. For each patient, imaging and pathology reports were reviewed to identify patients with neuroendocrine tumor liver metastases that were treated with embolization. Exclusion criteria were: patients with prior locoregional therapy (liver ablation or radioembolization) and patients who received ablation at the time of initial embolization.

Based on these criteria, 160 patients with NET liver metastases were identified: 77 patients were initially embolized using < 100-μm spherical particles, and 83 patients were initially embolized using only ≥ 100-μm spherical particles. Average age at the time of initial locoregional therapy was 59, and 53% of patients were male.

Transarterial Embolization Technique

Transarterial embolization was performed by a board-certified, fellowship-trained interventional radiologist, under moderate sedation, monitored anesthesia care, or general anesthesia. Embolization was performed using spherical particles: Embospheres (40–120 μm or 100–300 μm, Merit Medical, South Jordan, Utah), Bead Block (100–300 μm, BTG, London, UK), or Embozene (100 μm, Boston Scientific, Marlborough, Massachusetts). Embolization was performed to stasis, which sometimes required the use of larger particles. Patients with bilobar disease underwent staged treatment, with right and left lobe treatments performed 4–8 weeks apart.

Patients received octreotide 250 mcg SC pre-procedure. Patients also received cefazolin 1 g IV, but patients with a history of bilioenteric anastomosis or other biliary intervention received cefotetan 2 g IV, and patients with a cephalosporine allergy or severe penicillin allergy received clindamycin 900 mg IV and gentamicin 1.5 mg/kg IV. Post-procedure, patients with a history of biliary intervention received antibiotics for 5 days and were discharged with ciprofloxacin 500 mg PO bid and metronidazole 500 mg PO tid.

Data Collection and Analysis

Response after the initial TAE was evaluated by mRECIST [10] on the first post-procedure CT or MRI, generally obtained 1 month post-treatment. Time to progression at any site was evaluated by mRECIST, after completion of the originally planned staged treatment (for example, right and left lobe embolization). Overall survival after initial TAE was evaluated. Post-procedure complications were classified as minor or major, based on guidelines from the Society of Interventional Radiology [11].

The following tumor and clinical variables were evaluated: primary site (lung, pancreas, small bowel, or other), tumor grade and degree of differentiation, volume of liver disease, the presence of extrahepatic tumor, the presence of NET-related symptoms, urgency of the initial procedure, age-adjusted Charlson comorbidity index at the time of initial locoregional therapy, numerical Child–Pugh score at the time of initial locoregional therapy, and ECOG performance status. The age-adjusted Charlson comorbidity

index provides an estimate of the risk of postoperative mortality due to age and comorbidities [12].

The following procedural variables were evaluated: smallest particle size used for TAE, degree of selectivity of the embolization, whether an extrahepatic vessel was embolized during the initial treatment, and angiographic evidence of arteriovenous shunting.

Proportions were compared using a chi-squared test or Fisher's exact test. Univariate logistic regression and multivariate logistic regression were performed to determine predictors of immediate response. Univariate and multivariate Cox proportional hazards model was used to determine predictors of time to progression and overall survival after initial locoregional therapy. Kaplan–Meier curves were compared using a log rank test. Statistical tests were performed in Mathematica 9 (Wolfram Research, Champaign, IL).

Results

Patient Characteristics

Patient characteristics are shown in Table 1. Most patients were Child–Pugh A, ECOG 0, had extrahepatic disease, and received lobar treatments.

Table 1 Patient characteristics

Total patients	160
Primary site	
Lung	8 (5%)
Pancreas	68 (43%)
Small bowel	40 (25%)
Other or unknown	44 (28%)
Degree of differentiation/grade	
Well differentiated, low grade	99 (62%)
Well differentiated, intermediate to high grade; or moderately differentiated	46 (29%)
Poorly differentiated or undifferentiated	7 (4%)
Unknown	8 (5%)
Charlson comorbidity index (age adjusted)	6.4
Child–Pugh score	5.2
ECOG performance status	
0	144 (90%)
1	14 (9%)
2	2 (1%)
$<$ 100-μm particles used	77 (48%)
Arteriovenous shunt on angiography	4 (3%)
Particle embolization of extrahepatic vessel at initial treatment	9 (6%)
Extrahepatic disease	127 (79%)
Disease volume $\geq$ 50% of liver	59 (37%)
Degree of selectivity	
Lobar	126 (79%)
Selective	34 (21%)
Symptomatic or functional NET	77 (48%)
Urgent inpatient treatment	4 (3%)
Additional therapy	
Radioembolization	4 (3%)
Ablation	2 (1%)
Liver resection	20 (13%)
Primary resection	43 (27%)
PRRT	18 (11%)
Somatostatin analogue	58 (36%)
Everolimus	21 (13%)
Sunitinib	7 (4%)
Cytotoxic chemotherapy	29 (18%)

Table 2 Complications after TAE on a per-patient basis

	< 100 μm	≥ 100 μm	*p*
Major complications	15 (19%)	23 (28%)	0.27
Minor complications	10 (13%)	13 (16%)	0.66
No complications	52 (68%)	47 (57%)	

Patients who had both minor and major complications are only recorded as major complications in this table

Table 3 Initial response to treatment (mRECIST) after TAE using particles < 100 versus TAE using only particles ≥ 100 μm

	< 100 μm	≥ 100 μm	All patients
CR	10 (13%)	10 (12%)	20 (13%)
PR	39 (51%)	25 (30%)	64 (40%)
SD	10 (13%)	28 (34%)	38 (24%)
PD	18 (23%)	20 (24%)	38 (24%)
Total	77	83	160

Patients who received particles < 100 μm had a higher initial response rate (CR + PR, Fisher's exact test, $p = 0.007$)

Complications

There was no difference in complications after TAE using < 100 vs ≥ 100-μm spherical particles (Table 2). Major complications were: post-embolization syndrome requiring prolongation of hospital stay by > 24 h ($n = 25$), dyspnea ($n = 8$), hypertensive urgency ($n = 3$), liver abscess requiring drainage ($n = 3$), altered mental status ($n = 2$), acute cholecystitis ($n = 2$), atrial fibrillation ($n = 2$), aspiration pneumonia ($n = 1$), bacteremia ($n = 1$), contrast-induced nephropathy ($n = 1$), and pulmonary edema ($n = 1$). Minor complications were: post-embolization syndrome ($n = 15$), dyspnea ($n = 4$), access site bleeding or bruising ($n = 3$), aspiration pneumonia ($n = 1$), asymptomatic celiac artery dissection ($n = 1$), chest pain ($n = 1$), and atrial fibrillation ($n = 1$). Some patients had multiple complications.

Table 4 Univariate logistic regression and multivariate logistic regression to predict immediate response (CR or PR) by mRECIST

	Univariate		Multivariate	
	OR	*p*	OR	*p*
< 100-μm particles used	2.4	0.0070*	2.2	0.025*
Primary site				
Lung	0.93	0.86		
Pancreas	0.90	0.71		
Small bowel	2.6	0.012*	2.2	0.063
Other or unknown	1			
Degree of differentiation/grade				
Well differentiated, low grade	2.1	0.017*	1.3	0.50
Well differentiated, intermediate to high grade; or moderately differentiated	0.79	0.48		
Poorly differentiated or undifferentiated	0.33	0.033*	0.15	0.11
Unknown	1			
Charlson comorbidity index (age adjusted)	0.94	0.30		
Child–Pugh score	0.86	0.60		
ECOG performance status	1.5	0.34		
Arteriovenous shunt on angiography	0.29	0.28		
Particle embolization of extrahepatic vessel at initial treatment	1.8	0.41		
Extrahepatic metastases	0.37	0.013*	0.43	0.067
Disease volume ≥ 50% of liver	0.30	0.00024*	0.40	0.015*
Degree of selectivity				
Lobar	1			
Selective	1.1	0.80		
Symptomatic or functional NET	1.4	0.31		
Urgent inpatient treatment	0.29	0.28		

OR > 1 means the variable is associated with better response, and OR < 1 means the variable is associated with worse response. *OR* odds ratio. Variables with $p < 0.1$ in the univariate analysis were included in the multivariate analysis

*Statistically significant result

Table 5 Univariate and multivariate prediction of time to progression at any site after TAE (Cox proportional hazards model)

	Univariate		Multivariate	
	RR	*p*	RR	*p*
< 100-μm particles used	0.78	0.15		
Primary site				
Lung	1.2	0.57		
Pancreas	1.2	0.20		
Small bowel	0.44	< 0.001*	0.52	0.0042*
Other or unknown	1			
Degree of differentiation/grade				
Well differentiated, low grade	0.64	0.010*	1.3	0.51
Well differentiated, intermediate to high grade; or moderately differentiated	1.4	0.076	1.9	0.13
Poorly differentiated or undifferentiated	5.0	< 0.001*	6.4	0.0014*
Unknown	1			
Charlson comorbidity score (age adjusted)	1.0	0.92		
Child–Pugh score	1.1	0.46		
ECOG performance status	0.79	0.48		
Arteriovenous shunt on angiography	1.2	0.80		
Particle embolization of extrahepatic vessel at initial treatment	0.83	0.61		
Extrahepatic metastases	1.5	0.051	1.4	0.13
Disease volume ≥ 50% of liver	1.8	0.0011*	1.7	0.0088*
Degree of selectivity				
Lobar	1			
Selective	0.84	0.42		
Symptomatic or functional NET	0.78	0.15		
Urgent inpatient treatment	0.63	0.43		

Variables with $p < 0.1$ in the univariate model were included in the multivariate model

RR relative risk of death

Initial Response

Initial response by mRECIST is shown in Table 3. 53% of patients had a complete or partial response on imaging. However, TAE patients who received particles smaller than 100 μm had a higher initial response rate. Multivariate logistic regression showed that use of particles < 100 μm and liver < 50% replaced with tumor were independent predictors of a better initial response rate (Table 4).

Time to Progression

Median time to progression at any site after TAE was 10 months for well- to moderately differentiated NET and 3.4 months for poorly differentiated or undifferentiated NET. A multivariate Cox proportional hazards model showed that small bowel NET, well- to moderately differentiated NET, and disease volume < 50% of liver were independent predictors of longer time to progression (Table 5). There was no difference in time to progression after TAE using particles < 100 versus TAE using only particles ≥ 100 μm.

Overall Survival

Multivariate Cox proportional hazards model showed that well- to moderately differentiated NET, liver < 50% replaced by tumor, and lack of AV shunting were the only independent predictors of improved OS (Table 6). Median overall survival after TAE was 55 months for well- to moderately differentiated NET and 13 months for poorly differentiated or undifferentiated NET. For well- to moderately differentiated NET, overall survival (and 95% confidence interval) was 87% (80–92%) at 1 year, 66% (57–74%) at 2 years, 59% (48–67%) at 3 years, and 48% (35–60%) at 5 years. For poorly differentiated or undifferentiated NET, overall survival was 51% (12–81%) at 1 year, 34% (5–69%) at 2 years, 17% (1–53%) at 3 years, and 17% (1–53%) at 5 years.

Table 6 Univariate and multivariate prediction of overall survival after TAE (Cox proportional hazards model)

	Univariate		Multivariate	
	RR	*p*	RR	*p*
< 100-μm particles used	0.64	0.11		
Primary site				
Lung	1.7	0.25		
Pancreas	0.71	0.22		
Small bowel	0.70	0.25		
Other or unknown	1			
Degree of differentiation/grade				
Well differentiated, low grade	0.71	0.20		
Well differentiated, intermediate to high grade; or moderately differentiated	1.4	0.20		
Poorly differentiated or undifferentiated	3.2	0.013*	5.0	0.0012*
Unknown	1			
Charlson comorbidity score (age adjusted)	1.0	0.76		
Child–Pugh score	1.6	0.066	1.4	0.17
ECOG performance status	2.1	0.12		
Arteriovenous shunt on angiography	3.6	0.030*	7.5	0.0079*
Particle embolization of extrahepatic vessel at initial treatment	0.85	0.75		
Extrahepatic metastases	2.1	0.045*	1.4	0.44
Disease volume ≥ 50% of liver	3.1	< 0.001*	2.9	< 0.001*
Degree of selectivity				
Lobar	1			
Selective	0.41	0.055	0.35	0.073
Symptomatic or functional NET	0.85	0.55		
Urgent inpatient treatment	0.57	0.57		

Variables with $p < 0.1$ in the univariate model were included in the multivariate model

RR relative risk of death

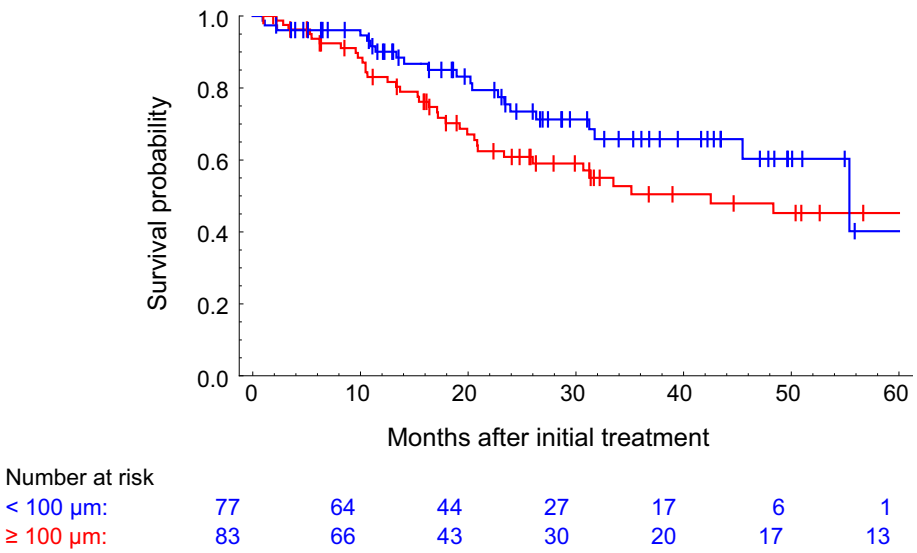

Fig. 1 Overall survival after initial TAE performed using < 100-μm particles (blue curve, 55-month median survival) versus only using ≥ 100-μm particles (red curve, 43-month median survival), $p = 0.11$

There was no significant difference in overall survival between TAE patients treated with < 100 versus only ≥ 100-μm particles (Fig. 1). In a multivariate Cox proportional hazards model, including all tumor, clinical, and procedural variables, use of < 100-μm particles did not affect survival (RR 0.89, $p = 0.73$).

Discussion

NET patients treated with TAE using 40–120-μm Embospheres had better initial response, but the same time to progression and overall survival, compared to TAE using only particles ≥ 100 μm. Thus, better initial response does not necessarily translate into better survival.

Several other studies have similarly shown that, for locoregional therapy, improved response often does not result in improved survival [13, 14]. The reason is unknown. Treatment toxicity could play a role, but in our study, there was no difference in complications between the two groups. Another possibility is that locoregional therapy can induce systemic effects that might counter the local benefits of the treatment [15]. One promising approach for improving survival (not just response) after locoregional therapy is the use of adjuvant medications that modulate these harmful systemic effects [15, 16].

There are some important caveats to the use of small particles (40–120-μm Embospheres) for embolizing liver tumors. The amount of 40–120-μm Embospheres should be limited to 5 syringes to limit potential shunting to the lungs, which can be fatal [17]. In addition, if there is concern for off-target embolization, then small particles should not be used [18].

The only independent predictors of improved overall survival after TAE were: well- to moderately differentiated NET, liver < 50% replaced by tumor, and lack of AV shunting. These factors were also found to be important in previously published studies [2, 19].

This study has several limitations. First, it is a small single-center retrospective study. Second, the ≥ 100-μm group included several different types of particles: 100–300-μm Embospheres, 100–300-μm Bead Block, and 100-μm Embozene. Third, the recent approval of PRRT [20] by the US FDA could affect the roles of TAE and RE in treating NET.

In conclusion, NET patients treated with TAE using particles < 100 μm had better initial response, but the same overall survival, compared to TAE using only particles ≥ 100 μm. The only independent predictors of improved overall survival after TAE or RE were: well- to moderately differentiated NET, liver < 50% replaced by tumor, and lack of AV shunting.

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Compliance with Ethical Standards

Conflict of interest FEB is a co-founder of Claripacs, LLC. He received research funding (investigator-initiated) and support for research meetings from Guerbet. He received research support (investigator-initiated) from GE. He received research supplies (investigator-initiated) from Bayer. He received a research grant and speaker fees from Society of Interventional Oncology, which were sponsored by Guerbet. He is an investor in Labdoor, Qventus, CloudMedx, and Notable Labs. AC is on the advisory board for Accurate Medical and is a stockholder in Amgen. EZ received an investigator-initiated industry research grant from Johnson & Johnson and has a pending investigator-initiated research grant from AAA-Novartis.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This HIPAA-compliant retrospective study was approved by the IRB.

Informed Consent For this type of study, informed consent is not required. This study has obtained IRB approval from Memorial Sloan Kettering Cancer Center, and the need for informed consent was waived.

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