

# Yttrium-90 Microspheres (SIR) vs Transarterial Chemoembolization (TACE) in Inoperable Metastatic Neuroendocrine Tumors (NETs)



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## BACKGROUND

Neuroendocrine tumors (NETs) are rare hormone secreting tumors that present with vague symptoms. At the time of diagnosis, most NETs have already metastasized to the liver. Greater than 90% of patients (pts) have inoperable liver disease. Transarterial chemoembolization (TACE), drug-eluting beads (DEB), and radioembolization (SIR) are effective based on tumor hypervascularity and predominant hepatic arterial blood supply. While each of these treatments have been shown to provide symptom control and improve progression-free survival, they have not been compared to each other. We attempted to compare the efficacy of SIR to TACE/DEB in the treatment of inoperable metastatic neuroendocrine tumor to the liver.

## METHODS

**Patients:** Medical records and axial imaging studies of pts with NET liver metastases and have undergone TACE, DEB, or SIR, were retrospectively reviewed from January 2001 to December 2010.

**Pre-Treatment Evaluation:** For patients undergoing TACE or DEB, a dual phase contrast-enhanced computed tomography (CT) of the abdomen and pelvis was completed. For SIR patients, a CT angiogram, followed by a planning angiogram with embolization of collateral vessels to prevent non-target site injury, and a 99m technetium-labeled macroaggregated albumin (<sup>99m</sup>Tc MA) hepatic perfusion scan to estimate the extent of hepatopulmonary shunting was completed. A hepatopulmonary shunt of >20% was considered prohibitive for SIR treatment.

**Modality:** TACE consists of a doxorubicin-oil emulsion followed by bland embolization using 300-700 micron beads. DEB consists of 300-500 micron beads admixed with 50mg doxorubicin. SIR uses SIRTeX SIR-Spheres®, which are 32 micron resins embedded with yttrium-90 ( $\beta$ -emitter). Radiation dose was calculated by taking into account tumor volume, body surface area, and the percentage of hepatopulmonary shunting.

**Treatment:** A procedure was defined as one patient encounter and a treatment was defined as all planned procedures to treat the intended tumor burden. If bilobar disease was present, the lobe with the largest tumor burden was treated first and the other lobe treated at a separate procedure. For TACE the emulsion is

injected until near stasis was achieved. For DEB and SIR, the full dose was given, unless near stasis was achieved first.

**Immediate Radiologic Assessment:** To measure both tumor size and perfusion, we elected to use both WHO and EASL criteria. Table 1 shows the numeric scores assigned to each objective response and the product of the two criteria together.

**Outcome Assessment:** Liver progression free survival was assessed after each treatment. Overall survival was determined at the time of last follow up.

**Table 1: Calculating Radiologic Response**

	Score	WHO	EASL
Complete Response (CR)	0	100% decrease in cross-product of target lesion(s)	100% decrease in amount of enhancing tissue in target lesion (s)
Partial Response (PR)	1	≥ 50% decrease in cross-product of target lesion(s)	≥ 50% decrease in amount of enhancing tissue in target lesion(s)
Stable Disease (SD)	2	< 50% decrease to ≤ 25% increase in cross-product of target lesion (s)	< 50% decrease in amount of enhancing tissue in target lesion(s)
Progressive Disease (PD)	3	>25% increase from maximum response of target lesion(s)	>25% increase in amount of enhancing tissue in target lesion(s) and/or new enhancement in previously treated lesions warranting further locoregional therapy

WHO x EASL score	Response
0	Complete Response (CR)
1-3	Partial Response (PR)
4	Stable Disease (SD)
>4	Progressive Disease (PD)

## RESULTS

**Patient Characteristics:** 41 pts with NET liver metastasis underwent 57 treatments (89 procedures) with a mean follow up of 26 months. TACE/DEB pts underwent a mean of 2.26 procedures/pt, while SIR pts underwent a mean of 2.05 procedures/pt. Pt characteristics are summarized in Table 2.

**Immediate Radiologic Assessment:** Radiologic assessment of treatment effect within the first 1-3 months shows an total benefit (CR+PR+SD) favoring SIR. Table 3.

**Overall Survival:** At a median follow-up of 81 months, overall 5 and 10-yr survival rate for TACE/DEB was 95% and 63%, and for SIR was 94% and 72%, respectively (NS). This included numerous patients with extrahepatic progression at the time of last follow up (TACE/DEB: 73.9%, SIR: 55.6%). On univariate analysis primary tumor resection improved overall survival (odds ratio [OR] = 0.21, 95% CI, 0.05-0.9), but this was not significant on multivariate analysis (OR =0.04, 95% CI, 0.0-1.45).

**Liver Progression Free Survival:** Treatment with SIR had a significant benefit on liver progression free survival compared to DEB/TACE (OR = 0.14, 95% CI =0.03-0.75) on multivariate analysis. The 2 year liver progression free survival for TACE/DEB was 48% (0.27-0.66, 95% CI) compared to SIR at 89% (0.62-0.97, 95% CI), Fig 1

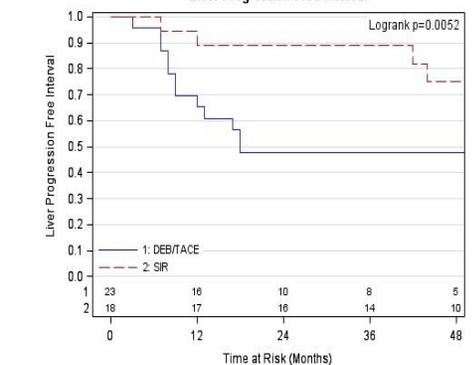
**Table 2: Patient Characteristics**

Characteristics	TACE/DEB (n = 23)	SIRs-Sphere (n = 18)	Overall (n = 41)	P-Value
Median Age at Diagnosis	57 (41-71)	53 (43-78)	56 (41-78)	
Gender (M/F)	14/9	13/5	27/14	0.447
ECOG PS (0/1)	20/3	15/3	35/6	0.745
Grade				0.556
Well – Diff	19 (82.6%)	14 (77.7%)	33 (80.5%)	
Poorly – Diff	1 (4.3%)	2 (11.1%)	3 (7.3%)	
unavailable	3 (13.0%)	2 (11.1%)	5 (12.2%)	
Primary Location				0.567
Pancreas	10	5	15	
Small Bowel	8	8	16	
Unknown	3	2	5	
Large Bowel	1	1	2	
Stomach	1	0	1	
Lung	0	2	2	
Primary Res (Y/N)	10/13	15/3	25/16	0.009
Synchronous / Metachronous	19/4	13/5	32/9	0.425
Extrahepatic Disease				
LN	15 (65.2%)	15 (83.3%)	30 (73.2%)	0.194
Peritoneal Dx	4 (17.4%)	5 (27.8%)	9 (22.0%)	0.425
Distant Dx	3 (13.0%)	1 (5.6%)	4 (9.8%)	0.423
Mean Time of Mets Dx to Tx (mos)	18.2	43.7		<0.001
Mean somatostatin Tx Duration (mos)	1.2	1.7		0.001

**Table 3: Procedure Characteristics and Response**

	TACE/DEB	SIRs-Sphere	P-Value
N procedures	54	35	
Technical Success	100%	100%	
Liver Involvement			
< 25%	18 (33.3%)	23 (65.7%)	0.007
> 25%	32 (59.3%)	9 (25.7%)	
Miliary	4 (7.4%)	3 (8.6%)	
LOS days (range)	1 (1-8)	0 (1-2)	<0.001
Immediate Radiologic Response (WxE)			
CR	0	3 (9.1%)	
PR	18 (37.5%)	16 (48.5%)	
SD	22 (45.8%)	13 (39.4%)	
PD	8 (16.7%)	1 (3.0%)	
Total Benefit	40 (83.3%)	32 (97%)	0.055
Mean Time to Liver Progression (mos)	36.4	60.4	<0.001

**Figure 1: Liver Progression Free Interval**



## CONCLUSIONS

Patients with NETs liver metastasis treated with SIR had more durable response than TACE/DEB (2-yr liver progression free interval: 89% vs 48%). Due to the retrospective nature and inherent selection bias of the current study, future studies controlling for resection of the primary tumor, time from diagnosis to liver-directed therapy, liver disease burden, and length of somatostatin treatment are needed to validate these findings.