Radioembolization for Metastatic Neuroendocrine Tumors

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Abstract

Transarterial radioembolization (TARE) using β-emitting yttrium-90 microspheres has been used for decades in patients with liver-dominant unresectable metastatic neuroendocrine tumors (mNETs). TARE is one of the embolotherapies supported by the National Comprehensive Cancer Network, among other guidelines, for progressive or symptomatic liver-dominant mNETs. Initial studies with relatively short-term follow-up have indicated that TARE is likely to be at least as effective in controlling symptoms and/or disease progression in the liver as bland or chemoembolization. However, more recent data have shed new light on the risk of long-term hepatotoxicity in patients with mNETs treated with TARE. In this article, we will discuss rationale for TARE, clinical indications, outcomes, and toxicity, as well as new strategies to enhance efficacy of TARE while reducing its toxicity in the treatment of liver-dominant mNETs.

Keywords
- radioembolization
- yttrium-90
- neuroendocrine tumor

Neuroendocrine tumors (NETs) have been increasing in incidence in the last four decades, and gastroenteropancreatic NETs (GEP-NETs) are currently the second most prevalent gastrointestinal cancer after colon cancer.[1] The liver is the most common site of metastasis from NETs[2]: up to 75% of patients with advanced small bowel NETs, 85% of patients with pancreatic NETs, and 66% of metastatic lung NETs develop liver metastases during the course of their disease.[3,4] Neuroendocrine tumor liver metastases (NETLMs) are associated with a relatively poor prognosis[5,6] secondary to considerable morbidity from hormonal symptoms such as carcinoid syndrome[7,8] or tumor bulk which can ultimately lead to liver failure.[9]

In patients who are not surgical or ablation candidates, hepatic intra-arterial therapies (IAT) including transarterial bland embolization (TAE), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) are indicated to reduce tumor burden, slow down the growth or progression of the disease, and improve quality of life by controlling symptoms related to tumor bulk and/or secretion of hormones.[10,11] There is generally no preference for the embolotherapies among interventional radiologists.[12] Despite early data suggesting that TARE has fewer short-term adverse events than other embolotherapies, concerns about chronic toxicity following TARE have emerged.[13]

In this article, we will explain the rationale behind using TARE for NETLMs; review the available data, including potential short- and long-term risks; and propose a new vision on how and where to use TARE in this patient population.

Rationale for Transarterial Radioembolization

Primary and secondary liver tumors receive the majority of their blood supply from the hepatic arteries rather than portal vein,[14] which make the liver a suitable organ for IATs. In addition, TARE relies on the increased vascularity of liver tumors to concentrate the radioactive microspheres preferentially into the terminal arterioles of tumors relative

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to normal liver parenchyma. Explanted livers treated with TARE (whether yttrium-90 (^{90}Y) resin or glass microspheres) demonstrated preferential accumulation of the radioactive microspheres mainly at the periphery and in nonnecrotic parts of tumors as opposed to normal liver parenchyma.[15,16]

NETLMs, especially from GEP-NETs, are usually hypervascular on arterial phase of multiphasic cross-sectional imaging,[17] which theoretically make them an ideal target of intra-arterial delivery of therapy. However, a basic approach of evaluating one time point of arterial hyperenhancement did not correlate with outcome of TARE in a small study of 17 patients with NETLMs.[18] This lack of correlation between tumoral enhancement at one time-point multiphasic imaging and post-TARE outcomes was also noted when studying 137 patients with multiple histologies (only 19 with NETLMs).[19] These findings could be related to the small number of patients included in these retrospective studies, wide variety of tumor types, different imaging characteristics and tumor enhancement depending on the site of origin,[17] and/or subjective basic imaging techniques used in determining tumor vascularity.[19]

Other more sophisticated techniques investigating arterial tumor enhancement fraction (the quotient of arterial phase enhancement divided by portal venous phase enhancement) predicted response to TARE in colorectal cancer.[20] Similarly, quantification of arterial perfusion (AP) in a heterogeneous patient population of mainly colorectal metastases yielded a 91% sensitivity and 95% specificity for predicting short-term morphologic response and 1-year survival with TARE.[21] In this study, AP determined by perfusion CT was the best single, independent predictor of survival with TARE as compared with multiphase CT and even ^{99m}Tc macroaggregated albumin (^{99m}Tc MAA) SPECT. This indicated that TARE is effective when administered to patients with a high AP irrespective of underlying primary malignancy or extension of hepatic metastatic disease.[21] Unfortunately, this study did not include any patients with metastatic NET, and therefore, extrapolation of the findings to NETLMs is limited. The majority of GEP-NETs are hypervascular as determined by angiography and basic enhancement pattern on cross-sectional imaging[17] (►**Fig. 1**). It is likely that well-circumscribed, uniformly hypervascular NETLMs are optimal candidates for TARE. The use of TARE in hypovascular NETLMs should be done carefully, and likely reserved for patients having rapidly progressing disease.

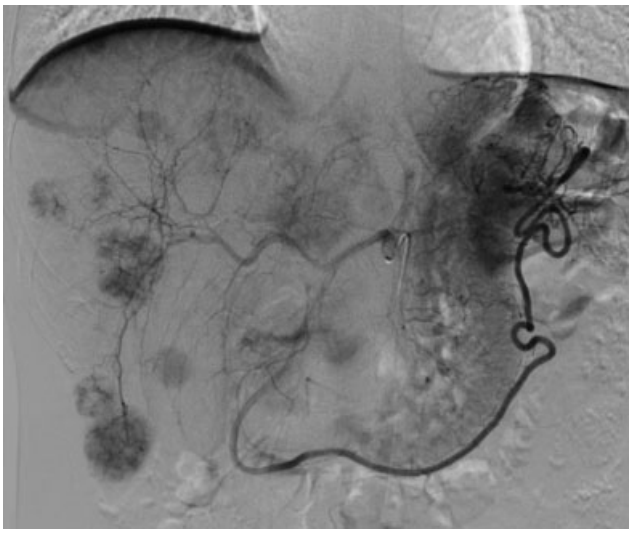

Fig. 1 Multifocal bilobar hypervascular liver lesions in a 50-year-old woman with metastatic pancreatic neuroendocrine tumor. Most neuroendocrine tumor liver metastases are hypervascular making them suitable for intra-arterial therapies.

Mechanism of Action

TARE relies predominantly on the radiation effect, with a minor contribution from microembolization.[22] ^{90}Y is a pure β-emitting isotope with an average energy of 0.9367 MeV, a mean tissue penetration of 2.5 mm and a maximum tissue penetration of 11 mm.[23,24] ^{90}Y has a physical half-life of 64.2 hours. This allows the delivery of high radiation doses to hepatic tumors with a "cross-fire"[25] mechanism between the ^{90}Y microspheres. The absorbed dose in the tumors and liver depends on hemodynamics and intratumoral vessel density,[26] with preferential implantation of the microspheres at the periphery of tumors[16] in the terminal arterioles.[25] The deposition of microspheres in the tumors in comparison to normal liver is variable with tumor to normal (T:N) ratio ranging between 3:1 and 20:1, but in general liver metastases have a T:N between 4 and 5.[21,27] The antitumoral effect of ^{90}Y relies on adequate oxygenation of targeted tissue[28] and is thought to be secondary to irreversible damage to tumor epithelial, stromal, and endothelial cells.[29] The characteristics of the two approved TARE devices in the United States, the ^{90}Y glass microspheres (TheraSphere; Boston Scientific, Marlborough, MA) and ^{90}Y resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia), are presented in ►**Table 1**.

Patient Selection

The goal of TARE, like other IATs, is to "reset the clock" in NETLMs, control progression of liver disease and local mass effect, reduce hormonal symptoms, reduce risk of carcinoid heart disease, and delay liver failure. The indications for use of TARE in NETLMs include:

- Liver-dominant disease.
- Progressive liver disease.
- Uncontrolled hormonal production despite use of somatostatin analog (SSA).
- Symptoms from bulky disease (i.e., abdominal pain, compression of vital structures such as bile ducts, portal vein; ►**Fig. 2**).

Exclusion Criteria

In general, patients are not considered good candidates for TARE if they have:

- Eastern Cooperative Oncology Group (ECOG) performance status >2.
- Elevated baseline bilirubin (>2 mg/dL), unless highly selective treatment can be performed.

Table 1 Characteristics of commercially available ^{90}Y microspheres in the United States

	^{90}Y glass microspheres	^{90}Y resin microspheres
Microsphere mean diameter	25 ± 10 μm	35 ± 10 μm
Matrix	Insoluble, biocompatible resin	Insoluble, biocompatible glass
Density	3.6 g/dL	1.6 g/dL
Mean radioactivity per microsphere at the time of calibration	2,500 Bq	50 Bq
Methods used to calculate activity to be injected	MIRD	BSA, partition model
Vials available with different activities	Standard: 3, 5, 7, 10, 15, 20 GBq Custom vials 3–20 GBq can be ordered at 0.5-GBq increments	3.0 GBq: day of calibration 4.3 GBq: 1 day precalibration 5.6 GBq: 2 days precalibration 7.3 GBq: 3 days precalibration
Spheres per vial	About 400,000 per GBq (i.e., 1.2 million for 3 GBq, 8 million for 20 GBq)	About 44 ± 2.6 million spheres in each delivery vial
Embolic effect	Minimal	Mild

Abbreviations: Bq, Becquerel; BSA, body surface area; GBq, gigabecquerel, MIRD, medical internal radiation dose.

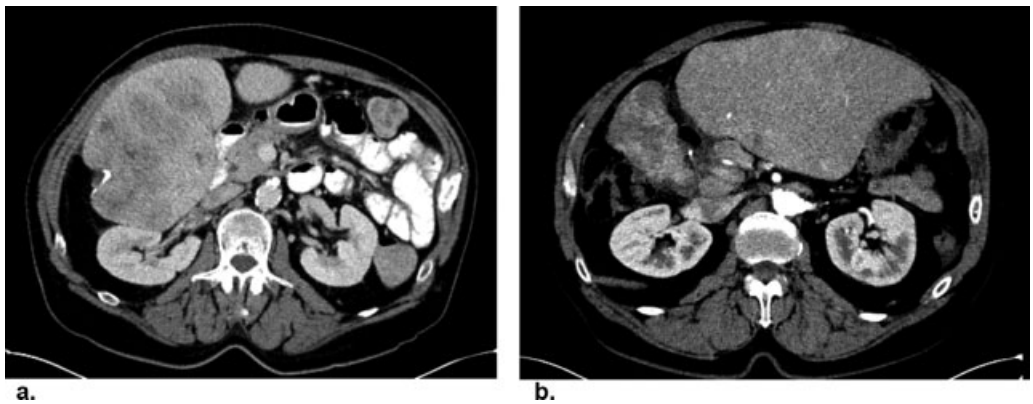

Fig. 2 A 57-year-old patient with metastatic pancreatic neuroendocrine tumor causing significant abdominal pain and partial gastric outlet obstruction treated with transarterial radioembolization (TARE). Pre-TARE contrast-enhanced CT scan demonstrates a large inferior right hepatic lobe neuroendocrine tumor metastasis causing significant mass effect with abdominal bulge, compression of the duodenum, and right kidney (**a**). The patient's right hepatic lobe received two administrations of 1 day precalibration ^{90}Y resin microspheres 1 month apart with a total activity of 4.43 GBq. The patient's partial gastric outlet obstruction and abdominal pain started improving 1 month posttreatment and completely resolved 3 months later. A 2-year post-TARE contrast-enhanced CT scan demonstrates significant shrinkage of the right hepatic lobe and tumor with resolution of mass effect (**b**).

- Alanine aminotransferase or aspartate aminotransferase $>5 \times$ upper limit of normal.
- Tumor burden >70% of the target liver volume, or tumor nodules too numerous to count.
- Tumor volume >50% combined with an albumin <3 g/dL.

After a patient is determined to be a candidate for TARE, a workup hepatic angiography followed by intrahepatic administration of ^{99m}Tc-MAA (100–150 MBq) is performed to determine tumor deposition, vascular anatomic variants, the presence of extrahepatic vascular collaterals, and the lung shunt fraction (LSF).[24,30,31] ^{99m}Tc-MAA particles are used as a surrogate to ^{90}Y microspheres since the mean diameter is 35 μm. The absolute contraindications for the use of ^{90}Y microspheres following the workup angiography and ^{99m}Tc-MAA scintigraphy include:

- Significant hepatopulmonary shunting with an expected radiation dose to the lungs >30 Gy in a single treatment or 50 Gy in multiple treatments.
- Extrahepatic collaterals supplying the gastrointestinal tract that cannot be avoided or coiled.

In addition, there are several relative contraindications that should be taken into consideration on individual basis including:

- Compromised pulmonary function.
- Inadequate liver reserve with ascites or encephalopathy.
- Serum creatinine >2.0 mg/dL.
- Platelet count $< 50 \times 10^9$/L.
- Severe iodinated contrast allergy.
- Life expectancy less than 3 months.

Table 2 Different methods to calculate the ^{90}Y microsphere activity to be administered in the liver

	MIRD	BSA	Partition
Main factors affecting prescribed activity	a. Perfused liver mass to be treated b. LSF	a. BSA b. % of tumor involvement	a. T:N ratio b. Target dose to tumor c. Mass of tumor(s) d. Mass of normal liver e. LSF
Compartment method	Unicompartment		Multicompartment
A calculation (GBq)	$= \frac{[\text{target dose (Gy)} \times \text{target liver mass (kg)}]}{50 \times (1 - \text{LSF})}$	$= [\text{BSA (m2)} - 0.2] + \frac{Vt}{Vt + Vn}$	$= Dn\ (Gy)\frac{\frac{T}{N} \times Mt\ (kg) + Mn\ (kg)}{50\ \left(\frac{J}{GBq}\right) \times (1 - \text{LSF})}$

Abbreviations: A, activity; BSA, body surface area; Dn, dose to normal tissue; LSF, lung shunt fraction; MIRD, medical internal radiation dose; Mn, mass of normal liver; Mt, mass of tumor(s); T:N, tumor to normal ratio; Vn, volume of normal liver tissue; Vt, volume of tumor(s).

- Tumor burden less than 20% for bilobar treatment.

While most of these inclusion and exclusion criteria are similar to TAE/TACE, a major difference is that portal vein thrombosis (PVT) is not a contraindication to TARE because the embolic effect is minimal compared with TAE/TACE. In patients with bilobar disease, the liver is treated one lobe at a time in 4 to 6 weeks apart as long the patient has recovered from initial embolization.

Dosimetry

Radioembolization treatment planning for ^{90}Y glass microspheres (TheraSphere; Boston Scientific) and ^{90}Y resin microspheres (SIR-spheres; Sirtex Medical) is quite different, but in both cases relies on semi-empirical methods. Currently, the radiation activity determination for ^{90}Y resin microspheres is based mostly on body surface area (BSA), and to a lesser extent on the multicompartmental partition model (PM). The BSA model is most commonly used due to its simplicity, as it assumes a theoretical liver volume, and the modified BSA model takes into account the percentage of tumor involvement.[32] The BSA model has been used in multiple randomized clinical trials with acceptable toxicity profile.[33] However, this method is criticized as it can lead to patients being either over- or underdosed. The PM is more personalized, as it incorporates the T:N uptake ratio, but is used less widely as it is a bit more complex. The PM is criticized for assuming uniform distribution of microspheres in the normal liver and tumors; for practical reasons, the T:N ratio is usually estimated rather than calculated. Radiation activity determination for ^{90}Y glass microspheres is based on the medical internal radiation dose (MIRD) model, which is a unicompartmental model assuming uniform distribution of microspheres in the perfused volume.[32] This can result in a wide variation of dose delivered to the tumors and normal liver parenchyma depending on the tumor burden and vascularity of the lesions. Similar to BSA, the MIRD model has been used for ^{90}Y glass microspheres with acceptable toxicities.[34,35] The different ^{90}Y microspheres activity calculation models are presented in ►**Table 2**.

There is a growing interest in voxel-based dose calculation treatment planning software.[36,37] A voxel-based dosimetry relies on the counts emitted from a three-dimensional pixel on a post-TARE positron emission tomography (PET; or single photon emission tomography [SPECT]) scan. Multiple companies have received clearance by the U.S. Food and Drug Administration (FDA) for this purpose. Ideally, a pre-TARE estimation of microsphere distribution would be able to better predict the dose distribution. However, ^{99m}Tc-MAA, the only currently available surrogate to ^{90}Y microspheres, has many limitations, including a percentage of particles outside the 10- to 90-µm range, particle breakdown, and overestimation of LSF.[38–40] Most importantly, ^{99m}Tc-MAA distribution may not exactly model ^{90}Y microsphere distribution. Many studies showed weak correlation between ^{99m}Tc-MAA SPECT and distribution of ^{90}Y resin microspheres in metastatic colorectal cancer (mCRC),[38,41,42] while others showed better correlation in predicting response and survival in patients with HCC when using ^{90}Y glass microspheres.[43–45] This inconsistency in correlation is possibly related to the difference in the number of microspheres, the embolic effect of resin microspheres, and differences in tumor perfusion. NETLMs have an enhancement pattern closer to HCC than mCRC. However, it is unclear whether there is a strong correlation between the distribution of ^{99m}Tc-MAA and ^{90}Y glass or resin microspheres when treating NETLMs. While data related to dose distribution in the treatment of NETLMs are still lacking, a small study of 15 patients with NETLMs treated with ^{90}Y resin microspheres found that an estimated tumor-absorbed dose $\geq$191.3 Gy predicted response by modified Response Evaluation Criteria in Solid Tumors (mRECIST) with 93% specificity and 83% specificity.[46] In this study, the absorbed dose was estimated using PM following manual volumes of interest on ^{99m}Tc-MAA SPECT/CT to determine T:N ratio. Twenty-five of 26 tumors (96.2%) responded when absorbed dose was $\geq$191.3 Gy compared with only 5 of 19 (26.3%) responders

Table 3 Most common imaging guidelines used to assess response following TARE

Guidelines	Definition	Classification
WHO[84]	Largest area: bidimensional tumor measurement	CR: 100% decrease in area of target lesion(s) PR: ≥50% decrease in area of target lesion(s) SD: <50% decrease to ≤25% increase in area of target lesion(s) PD: >25% increase in area from maximum response of target lesion(s) and/or new lesion(s)
RECIST[85]	Longest diameter: unidimensional tumor measurement	CR: 100% decrease in longest diameter of target lesion(s) PR: ≥30% decrease in longest diameter of target lesion(s) SD: <30% decrease to ≤20% increase in longest diameter of target lesion(s) PD: >20% increase in maximum diameter from maximum response of target lesion(s) and/or new lesion(s)
mRECIST[86]	Longest diameter of enhancing tissue: unidimensional measurement	CR: 100% decrease in enhancing tissue of target lesion(s) PR: ≥30% decrease in enhancing tissue of target lesion(s) SD: <30% decrease to ≤20% increase in enhancing tissue of target lesion(s) PD: >20% increase in enhancing tissue from maximum response of target lesion(s) and/or new enhancing lesion(s)

Abbreviations: CR, complete response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progression of disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TARE, transarterial radioembolization; WHO, World Health Organization.

when dose was less than 191.3 Gy. An absorbed tumor dose less than 72.8 Gy predicted no response.[46]

Imaging Assessment of Tumor Response

Multiphasic CT and MRI are the most commonly used standard imaging modalities to evaluate NETLMs response following TARE. Imaging interpretation guidelines include World Health Organization (WHO), RECIST, and mRECIST.[47–49] By focusing on the enhancing viable tumor based on arterial enhancement using contrast-enhanced studies, mRECIST addresses the shortcomings of WHO and RECIST which are more suited to evaluate systemic therapies rather than locoregional therapies such as TARE. The most common imaging guidelines to assess response to TARE are summarized in ►**Table 3**.

Data on Transarterial Radioembolization

Only a single pilot study of 11 patients with small bowel NETLMs randomized patients to TAE versus TARE, but the small sample size was inadequate to compare the two treatments.[50] Otherwise, no randomized trials have studied the effect of TARE in NETLMs, and the degree of evidence for TARE is considered by the National Comprehensive Cancer Network (NCCN) as category 2B (based on lower-level evidence, there is consensus that the intervention is appropriate).[13] Most cohort studies included data on NETLMs within a mixed population of non-NET tumor types, and the ones that focused on NETLMs comprised mostly a small number of patients, heterogeneous tumor types, with lack of details on primary tumor site and/or grading.[49,51] Most data from cohort studies on TARE and NETLMs come from ^{90}Y resin rather than glass microspheres,[48,49,51–56] with no standardized follow-up, and inconsistency in reporting both objective response rates (ORRs) and survival.[49] Therefore, the systematic review and meta-analyses that resulted from these publications were also limited, as they included multi-institutional studies which resulted in inclusion of overlapping patients.[49,51–53]

Radiographic Response

Determination of radiographic response varies between studies depending on imaging criteria used and the time of imaging. Kennedy et al[57] reviewed 148 patients from 10 different institutions and reported 3-month radiologic response, finding an ORR of 63.2% (60.5% PR; 22.7% SD; 4.9% PD) and a disease control rate (DCR) of 65.1% (60.5% PR; 4.9% PD). However, imaging criteria used to assess response was based on either RECIST or WHO when possible, or best radiographic estimate.[57] In addition, stratification by prognostic factors such as tumor grade or primary tumor site was lacking in this study. A systematic review of 870 patients by Jia and Wang[53] reported that median DCR at 3 months was 86% (range: 62.5–100%) when using RECIST or WHO criteria. With a median follow-up of 25 months (range: 11.9–60 months) after TARE, the reported median values for complete response, partial response, stable disease, and progressive disease were 2.7% (range: 0–15%), 35.3% (range: 12.5–66.5%), 40% (range: 14.7–75%), and 14% (range: 0–37.5%), respectively.[53] A more recent study using RECIST 1.1 by Tsang et al[55] reported 0% CR, 53% PR, 33% SD, 12% PD, and 2% unknown, which are comparable to previous results.[58]

A recent large retrospective multicenter study by Braat et al[48] reviewed 244 patients and reported 3- and 6-month ORR of 15.7 and 28.5%, respectively, with a DCR of 91.3 and 91.4%, respectively, when using RECIST v1.1. When modified RECIST (mRECIST) was used, the 6-month ORR was 62.9% with DCR of 91.4%.[48] This is in line with publication by Zuckerman et al[56] which also used mRECIST and found 5.1% CR, 45.8% PR, 30.5% SD, and 6.8% PD response rates.

Symptom Control

With regard to symptom control, Braat et al[48] reported an overall response in 79% of patients; 44% had complete response and 35% had partial response.[48] In the systematic review by Jia and Wang,[53] 69% of patients had improvement in their carcinoid syndrome . These results are comparable to TAE (64–93%), and TACE (60–95%) in terms of symptomatic improvement.[59] Engelman et al found no difference in the rate of symptom control between TAE, TACE, and TARE.[60]

Survival

A meta-analysis and systematic review by Frilling et al[52] and Jia and Wang,[53] evaluating 19 and 11 retrospective studies, found a median general OS of 28 months (range: 14–70 months) and 32 months (range: 18–57 months) after TARE, respectively. When stratified by tumor types, the median OS for patients with small bowel, pancreatic, and unclassified NETs were 56, 31, and 28 months, respectively, and when stratified by tumor grade, median OS for grade I, II, and III NETs were 71, 56, and 28 months, respectively.[53] These results should be interpreted with caution since up to 19.8% (77 out of 388) of patients in the 11 studies reviewed by Jia and Wang[53] underwent TAE or TACE before TARE.

In 2017, Chen et al[54] presented the results of a multicenter retrospective study of 155 patients with NETLMs from different sites, mostly pancreas ($n = 71$) and gastrointestinal ($n = 68$), who were treated with TACE ($n = 50$), TARE ($n = 64$), or TAE ($n = 41$). In this large retrospective study with propensity score analysis, there was no significant difference between embolotherapies, and no difference between ^{90}Y resin ($n = 43$) and glass ($n = 21$) with a hepatic progression-free survival (HPFS) of 14.9 and 23.4 months, respectively. With regard to post-TARE OS, the results were similar to prior TARE-only series,[47,57,61,62] with no difference between resin (48.2 months) and glass TARE (51.6 months). However, interestingly there was a trend toward worsened prognosis with TARE versus TACE,[54] which was seen in a previous study comparing these two treatment modalities.[63]

Tsang el al[55] reported on 49 patients treated mostly with ^{90}Y resin TARE (SIR-Spheres 69%, TheraSphere 29%, 2% unknown; between June 2011 and January 2017 across six regional centers in British Columbia, Canada). The median OS of this group was 27.2 months (95% CI: 8.0–46.5), which is comparable to previously reported outcomes that measured from 22 to 70 months.[58]

More recently, Braat el al[48] reported the results on ^{90}Y resin microspheres from eight different institutions in the United States and Europe that found a median OS after TARE for NETLMs of 31.2 months (range: 1.7–144 months; 95% CI: 26.4–36 months). This study provided more data on NETLMs from different primary sites and grades, and found, as expected, a shorter OS for higher grades ($p < 0.001$): median OS was 37.2 months (95% CI: 31.2–44.4), 28.8 months (95% CI: 22.8–36), and 10.8 months (95% CI: 1.2–22.8) in G1, G2, and G3 NET/neuroendocrine carcinoma (NEC), respectively.

Zuckerman et al[56] reported on 59 patients from a single academic center who were treated between 2009 and 2015 mostly with TARE (SIR-Spheres 64%, TheraSphere 46%; mean administered activity 1.71 and 5.43 GBq, respectively). Median HPFS was 18 months (95% CI: 13–27) and the median OS was 31 months (95% CI: 27 months to unreached).

Factors that are commonly found to be predictive of better OS after TARE are female gender, well-differentiated tumor, low K_i-67, good performance status, low hepatic tumor burden, and absence of extrahepatic metastases.[48,53–55]

A recent two-institution retrospective analysis showed no difference on long-term PFS or OS between TACE and TARE, despite TACE showing a greater DCR.[64]

Toxicity

Short-term toxicities following TARE have been described as minor, and in 2015 a multidisciplinary group of experts convened to form the NET-Liver-Metastases Conference that reviewed 11 reports on TAE or TACE and 7 on TARE.[49] In this meeting, TARE was considered to have advantages over TAE and TACE because of fewer side effects. However, the guidelines were based on data from small retrospective studies and included papers that either did not report on toxicity[65] or reported toxicity up to 6 months.[61,66] Most short-term side effects post-TARE, including abdominal pain (median: 32.6%, range: 2.7–100%), nausea/vomiting (median: 32.5%, range: 3.2–100%), and fatigue (median: 30.4%, range: 6.5–63%),[53] are mild and transient. Additionally, the most frequent hematological complications of TARE are lymphocytopenia (6.7%) and thrombocytopenia (3%).[48] More serious complications are less common (<1%) and usually related to nonrecognition of extrahepatic vascular collaterals and nontargeted embolization resulting in cholecystitis, gastrointestinal ulcers, and gastritis.[53,67,68] In Jia and Wang's systematic review, only one early death due to hepatic failure post-TARE was reported in more than 800 patients.[53] Patients who had previous biliary instrumentation have a higher risk for cholangitis and liver abscess after embolization due to bacterial colonization of the biliary tree. The risk of infectious complications is lower after TARE (~10%) than after TAE/TACE (~20%) despite broad-spectrum antibiotic coverage.[13,69] ^{90}Y glass microspheres appear to carry a higher risk than resin microspheres, which might be due to higher activity per glass sphere, and smaller size leading to deeper penetration.[69]

In the past 4 years, several reports have emerged about the risk for long-term hepatotoxicity after TARE.[70–72] This phenomenon was labeled as radioembolization-induced chronic hepatotoxicity,[71] occurring at least 6 months after TARE and manifesting as cirrhosis-like morphology, liver dysfunction, and ascites.[49,70,71,73] In a retrospective study of 39 patients with NETLMs treated with ^{90}Y glass and a follow-up of more than 2 years, Su et al[70] found that the median time to cirrhosis-like morphology was 1.8 years. This developed in 56.4% (22/39) of patients who received bilobar TARE, and even though there was no overall significant change in liver volume, the spleen did increase significantly

in size and the platelet and albumin decreased significantly over time. 41% (16/39) of patients developed ascites and 15.4% developed varices. These findings were supported by a retrospective review of 52 patients treated with ^{90}Y resin with more than 1 year of follow-up by Tomozawa et al[72] who found that new imaging changes of cirrhosis-like morphology or portal hypertension developed in 29% (15/52) of patients, most of who received bilobar treatment. In fact, the 29 patients who received bilobar TARE were more likely to develop cirrhosis-like morphology (6 patients [20.7%]), ascites (5 patients [17.2%]), splenomegaly (6 patients [20.7%]), and varices (2 [6.9%]), although this did not reach statistical significance. These reports lead to recent caution in NCCN guidelines with regard to routine use of TARE for bilobar NETLMs.[13]

In a comparative single-center retrospective study examining chronic hepatotoxicity after conventional TACE ($n = 63$) or ^{90}Y resin TARE ($n = 28$) for NETLMs at a minimum follow-up of 6 months, excluding patients with treatment crossovers and those who survived less than 1 year, there was higher chronic hepatotoxicity with TARE (bilobar in 71% of TARE cases), but without reaching statistical significance.[74]

There is scarcity of data linking the amount of absorbed radiation and hepatotoxicity in NETLMs. Zuckerman et al reported three potentially treatment-related deaths secondary to hepatic failure out of 51 patients with NETLMs treated with ^{90}Y resin.[56] Ten patients within the cohort underwent a posttreatment PET-MRI dosimetric analysis, and authors found that the patients who did not develop hepatotoxicity or hepatic fibrosis received a mean dose to normal liver of 25.4 Gy, while the mean liver dose in patients who experienced toxicity (hepatic fibrosis $n = 2$ and death from hepatic failure $n = 1$) was 59.1 Gy. Additional data are needed to determine the safe range of absorbed dose in normal liver to avoid liver toxicity while optimizing tumor response.

Combination with Chemotherapy

There are early phase 1 and 1b data on combining SIRT with everolimus and pasireotide,[75] and capecitabine-temozolomide.[76] These combination therapies hold promise and have so far proven safety. King et al[77] prospectively studied a combination of TARE and 7-day systemic infusion of 5-fluorouracil as a radiosensitizer in 34 patients with progressive NETLMs. Symptom control was noted in 55 and 50% of patients at 3 and 6 months, respectively. Using RECIST, the overall response rate (ORR) was seen in 50% of cases, with 18 and 32% showing a complete or partial response, respectively.[77] There was low toxicity in this combination, but the ORR is pretty similar to historical results of embolotherapies.

Sequencing with Peptide Receptor Radionuclide Therapy

In early 2018, the U.S. FDA approved ^{177}Lutetium (^{177}Lu)-DOTATATE for the treatment of somatostatin receptor–positive GEP-NETs.[78] This was based on the results of NETTER-1 trial comparing ^{177}Lu-DOTATATE with long-acting SSA to high-dose SSA alone in patients with progressive, well-differentiated locally advanced/inoperable or metastatic somatostatin receptor-positive midgut NETs.[79] It was also supported by data from Erasmus Medical Center, where a single-institution, single-arm, open-label trial evaluated ^{177}Lu-DOTATATE in patients with bronchial and GEP-NET somatostatin receptor-positive tumors.[80]

Sequencing of liver embolotherapy and peptide receptor radionuclide therapy (PRRT) has not been well established, and is based currently on institutional preference.

In view of the emerging data on long-term hepatotoxicity following TARE,[70,72] there is a concern about the potential additive effect of absorbed radiation by the liver in patients also receiving PRRT. A small retrospective analysis by Hamiditabar et al[81] looking at the safety of ^{177}Lu-DOTATATE PRRT following liver embolization in 51 patients (30 had prior TACE and/or TAE, 10 had prior TARE, and 11 had both) did not demonstrate a statistically significant increase in hepatotoxicity, but only 10 patients had prior TARE. In an earlier small case series, 10 of 17 heavily pretreated U.S. patients with embolotherapy followed by PRRT developed hepatotoxicity,[82] which raised the alarm on the risks of prior radiation exposure with ^{90}Y.

The efficacy and safety of ^{90}Y TARE after PRRT was addressed in a multicenter retrospective study by Braat et al.[83] Forty-four patients underwent 58 TARE procedures, of which 55% were to the whole liver, at a median of 353 days after prior PRRT. By RECIST 1.1 at 3 months, the ORR was 16% and DCR was 91%. Three patients developed

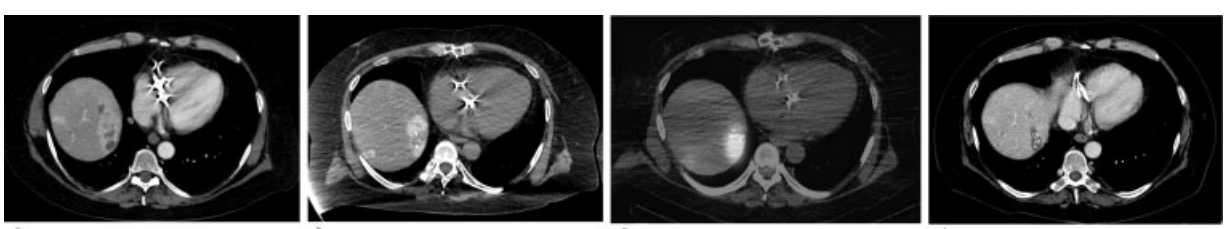

Fig. 3 A 58-year-old man with metastatic small bowel neuroendocrine tumor was referred for radiation segmentectomy of an enlarging mass in segment 7 of the liver. Pre–transarterial radioembolization contrast-enhanced CT scan demonstrates an arterially enhancing heterogeneous mass with areas of necrosis in segment 7 (**a**). A CT arteriogram performed during workup confirmed superselective perfusion of this lesion by segment 7 right hepatic artery branch (**b**). ^{99m}Tc MAA SPECT/CT shows intense localized activity in the tumor, significantly higher than the surrounding normal liver (**c**). After delivering 153 Gy of ^{90}Y glass microspheres in segment 7 branch, a 7-month follow-up CT scan demonstrates complete response of the tumor by modified Response Evaluation Criteria in Solid Tumors (mRECIST; **d**).

radioembolization-induced liver disease and one died 20 weeks after TARE.

General Recommendations for Use of TARE

Caution should be used in patients with low-grade, bilobar NETLMs who have a long life expectancy in view of the risk of long-term hepatotoxicity. Patients with relatively aggressive tumors, or those who have previously received TAE or TACE, may be appropriate candidates for TARE. Sequential bilobar or whole liver TARE should be avoided in many circumstances, unless exposure of normal liver parenchyma is predicted to be low. Superselective radiation segmentectomy with TARE is a good option in localized unresectable or unablatable tumors (►**Fig. 3**). Older patients are better served with TARE due to lower acute side effects compared with TAE/TACE. Patients with prior biliary instrumentation (Whipple surgery, sphincterotomy, biliary stent) are better served with TARE since risk of infectious complications is about half that with TAE/TACE despite broad-spectrum antibiotic coverage.

As opposed to TAE/TACE, retreating a lobe with ^{90}Y microspheres should be done with extreme caution after reviewing previously received dose due to increased risk of hepatotoxicity.

Conclusion

Decisions on the type of liver-directed embolotherapy have been traditionally been guided by institutional preference. After initial data were reported on the efficacy and short-term safety of TARE in NETLMs, longer-term follow-up shed light on potential hepatotoxicity. While additional prospective comparative studies are needed to define the optimal embolotherapy, TARE remains a valid treatment option, but should be given with caution. Due to the heterogeneity of NETs, a more personalized approach to the type of embolotherapy is needed, especially when using TARE. The advent of new TARE dosimetry software will potentially allow for more accurate activity prescription to deliver the optimal treatment dose into the tumor while preserving the normal liver parenchyma. Finally, more prospective data are required to improve patient selection and sequencing of TARE with other therapies.

Conflict of Interest
None declared.

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