Radioembolization Versus Bland or Chemoembolization for Liver-Dominant Neuroendocrine Tumors: Is it an Either/Or Question?

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Keywords: Neuroendocrine tumors; liver metastases; transarterial embolization; transarterial chemoembolization; transarterial radioembolization; selective internal radiation therapy

Running Title: TARE vs. TAE/TACE in liver dominant NETs

Disclosures:
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Ghassan El-Haddad MD: Curium Pharma and Oncoinvent AS (Advisory Board)
Taymeyah Al-Toubah MPH: None
Diane Reidy-Lagunes MD: Novartis, Merck, Ipsen (Research Funding); Advanced Accelerator Applications and Chiasma (Advisory Board)
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Arvind Dasari MD: Ipsen, Novartis, Hutchison Pharma, Guardant Health, Xencor, Eisai (Research Funding), Novartis, Advanced Accelerator Applications, Crinteics (Advisory Board)
Philip A. Philip MD PhD: Astrellas Pharma, Astra Zeneca, Bayer, BeiGene, BMS, Concept Therapeutics, Daiichi Sankyo Inc, Eisai, Gritstone, Incyte, IQVIA Biotech, Merck, Natera, NGM Biopharmaceuticals, Novocure, QED Therapeutics, Syncore, Taiho Oncology Inc, Thyme, Trisalus (Research Funding); Bayer, Incyte, Novartis (Speakers Bureau), Blueprint Medicines, Erytech (DSMB Committee); Caris Diagnostics, Daiichi Sankyo Inc, Ipsen, Merck, Novartis, Rafael Pharma (Advisory Committee); IQVIA Biotech, Syncore, Trisalus (Consulting)
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Hepatic arterial embolization has been used for decades to treat liver-dominant metastatic neuroendocrine tumors (NETs). During the 1970s-1990s, transarterial bland hepatic arterial embolization (TAEs) and chemoembolization (TACE) techniques were developed (1,2). Numerous studies have demonstrated high radiographic and symptomatic response rates among patients with NET liver metastases. More recently, transarterial radioembolization (TARE) has been introduced, a technique that uses Yttrium-90 ($^{90}$Y) glass or resin beads.(3)

As opposed to TAE and TACE, TARE does not rely on vascular occlusion and is considered microembolic; indeed, radiation-induced cytotoxicity requires adequate oxygenation of the targeted tissue (4).

Data on embolization for NETs have been primarily retrospective in nature. A previous randomized study comparing bland to chemoembolization was aborted due to poor accrual (5). Absence of prospective randomized data has spawned multiple institutional retrospective series comparing outcomes among patients treated with different embolization techniques (6-8). However, selection biases limit the interpretability of these data, and results have not consistently favored one technique. Consequently, institutional preferences rather than evidence-based data have generally guided the selection of embolization modality.

Although short-term toxicities associated with TARE are relatively minor, long-term data indicate a heightened risk of chronic radioembolization-induced liver disease, manifested by ascites, jaundice, and a pseudocirrhotic appearance to the liver (9-12). These side effects can develop 6 months to years after TARE and occur primarily in patients undergoing non-selective bilobar liver embolizations. Concerns about chronic liver toxicities have appeared in recent NET guidelines, including those of the National Comprehensive Cancer Network (NCCN), which warn about the routine use of TARE for patients with bilobar liver metastases (13). However, all discussions of TARE risks/benefits compared to conventional embolization are limited by the scarcity of high-level evidence.

Debates continue on the relative merits of TARE versus TAE/TACE. However, given the exceptional diversity of NETs in terms of tumor grade, primary site, vascularity, distribution within the liver, life expectancy, and rate of progression, the controversy over which technique is ‘superior’ is likely misdirected. A more clinically relevant question is under which particular circumstances should TARE be considered, and conversely, when should TAE/TACE remain the standard approach?
Several parameters favoring TARE over conventional embolization have already been described. One of these is history of prior biliary intervention such as Whipple surgery or biliary stenting in which the risk of a hepatic abscess (due to bacterial colonization of the biliary system) is substantially higher with conventional embolization than with TARE.\(^{[14,15]}\) Another factor is portal vein thrombosis or stenosis which is considered a relative contraindication to TAE/TACE but not for TARE \(^{[16]}\).

Other potential factors, which have not been as well described, can potentially influence treatment selection in favor of one type of embolization modality. These include the extent of disease, aggressiveness of tumor progression, prior and potential subsequent systemic treatments, and radiographic features of metastases, including vascularity and conspicuity.

Patients with scattered low volume liver metastases (e.g., <10-20% liver involvement) may be at excess risk of chronic radioembolization-related liver disease after TARE since much of the administered radiation may intersperse in the normal liver parenchyma (figure 1). Likewise, very high liver tumor volumes (e.g. >50%) may also predispose patients to chronic radiation hepatitis, given the wide dispersal of radiation throughout the liver. These problems may be exacerbated in patients with a long life expectancy who can potentially suffer the chronic effects of hepatic radiation injury years after embolization. While considerations of hepatic tumor volume also apply to conventional embolization, the toxicities tend to be acute rather than chronic. Risks of TAE/TACE in high tumor burden patients can be reduced by treating relatively small liver segments over multiple sessions.

Tumor vascularity and conspicuity are radiographic features to consider in the selection of therapy. For practical purposes, tumor avidity on arterial phase imaging of a CT or MRI scan can serve as a rough estimate of vascularity. Highly vascular tumors may absorb radioactive beads at a higher proportion than surrounding liver parenchyma. Indeed, one study of TARE in colorectal cancer determined that the degree of arterial tumor enhancement, measured as the arterial enhancement fraction, predicted response to radioembolization \(^{[17]}\). A small study of TARE in 17 patients with metastatic NETs reported a correlation between hypervascularity and ≥10% tumor shrinkage, a threshold used in Choi criteria \(^{[18]}\). Not all studies have confirmed that tumor vascularity using conventional imaging techniques is associated with embolization outcomes \(^{[19]}\). However, well-demarcated, non-
infiltrative hypervascular tumors are likely associated with enhanced absorption of beads compared to surrounding liver parenchyma, thus reducing damage to normal liver.

Patients with relatively localized tumors may benefit more from selective radiation delivery through TARE in the form of radiation segmentectomy or lobectomy. In unilobar radioembolization, the risks of clinically significant radioembolization-induced liver disease are low, and data suggest long-term disease control with little short or long-term toxicity (20). Tumoral aggressiveness can also influence the choice of therapy. Radiation is cell-cycle dependent (least active in G₀ and early G₁ phase and most active during G₂ and mitotic phase) and requires at least some degree of cellular proliferation for response (21-23). A single-center retrospective study suggested a selective benefit associated with TARE compared to bland embolization in intermediate-grade versus low-grade NETs (24). While not all studies confirm this association (25), TARE may be particularly beneficial when high doses of radioactivity can be selectively administered to rapidly progressive, localized tumors.

In summary, TARE may have advantages over TAE/TACE in certain circumstances, e.g., relatively localized, vascular tumors associated with a high degree of radioactive bead uptake compared to normal liver. Long-term TARE risks appear to be particularly concerning among patients with bilobar metastases, long life expectancy, and tumoral features associated with relatively low absorption of beads. Ultimately, more data are required to validate treatment selection parameters. However, to move beyond the question of which modality is ‘better,’ we need to refine our questions and investigate what factors favor which type of embolization modality.
References


Figure 1

Computed Tomography Scan before (left) and two years after (right) TARE in patient with low-volume liver disease