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

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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 (TAE) 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 ^{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. A previous randomized study comparing TAE to TACE was aborted because of 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 mo to years after TARE and occur primarily in patients undergoing nonselective bilobar liver embolizations. Concerns about chronic liver toxicities have appeared in recent NET guidelines, including those of the National Comprehensive Cancer Network, which warn about the routine use of TARE for patients with bilobar liver metastases (*13*). However, all discussions of TARE risks and benefits compared with 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 a 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 to 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 (Fig. 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 experience the chronic effects of hepatic radiation injury years after embolization. Although 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

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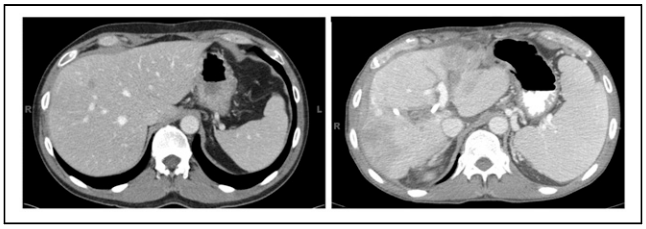

FIGURE 1. CT scan before (left) and 2 y after (right) TARE in patient with low-volume liver disease.

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 at least 10% tumor shrinkage, a threshold used in the Choi criteria (*18*). Not all studies have confirmed that tumor vascularity using conventional imaging techniques is associated with embolization outcomes (*19*). However, well-demarcated, noninfiltrative hypervascular tumors are likely associated with enhanced absorption of beads compared with 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 the G_0 and early G_1 phases and most active during the G_2 and mitotic phases) 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 with bland embolization in intermediate-grade versus low-grade NETs (*24*). Although 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, such as relatively localized, vascular tumors associated with a high degree of radioactive bead uptake compared with 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.

DISCLOSURE

Jonathan Strosberg is a consultant for Novartis and is on the speakers' bureau for Ipsen and Lexicon. Ghassan El-Haddad is on the advisory board for Curium Pharma and Oncoinvent AS. Diane Reidy-Lagunes receives research funding from Novartis, Merck, and Ipsen and is on the advisory board for Advanced Accelerator Applications and Chiasma. Etay Ziv has received research grants from Ethicon, Novartis, and Druckenmiller. Armeen Mahvash has received research funding from Sirtex Medical and Boston Scientific/BTG and is a consultant for ABK Biomedical. Arvind Dasari has received research funding from Ipsen, Novartis, Hutchison Pharma, Guardant Health, Xencor, and Eisai and is on the advisory board for Novartis, Advanced Accelerator Applications, and Crinteics. Philip Philip has received research funding from Astrellas Pharma, Astra Zeneca, Bayer, BeiGene, BMS, Corcept Therapeutics, Daiichi Sankyo Inc., Eisai, Gritstone, Incyte, IQVIA Biotech, Merck, Natera, NGM Biopharmaceuticals, Novocure, QED Therapeutics, Syncore, Taiho Oncology Inc., Thyme, and Trisalus; is on the speakers' bureau for Bayer, Incyte, and Novartis; is on DSMB committee for Blueprint Medicines and Erytech; is on the advisory committee for Caris Diagnostics, Daiichi Sankyo Inc., Ipsen, Merck, Novartis, and Rafael Pharma; and is a consultant for IQVIA Biotech, Syncore, and Trisalus. Michael Soulen has received research funding from Guerbert LLC and Boston Scientific and is a consultant for Guerbert LLC, Genentech, and Instylla. No other potential conflict of interest relevant to this article was reported.

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