

Transarterial Treatment of Liver Metastatic Neuroendocrine Tumors

Catheter-based therapies are effective for a diverse group of neoplasms.

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Neuroendocrine tumors (NETs) arise from neural and endocrine organs throughout the body, most commonly the gastrointestinal system and pancreas. The World Health Organization classifies well-differentiated gastroenteropancreatic NETs into low grade and intermediate grade, and most poorly differentiated tumors are considered high grade, based on mitotic count/Ki-67 proliferative index.¹ Indolent and well-differentiated tumors of the digestive system are traditionally called *carcinoid* and *pancreatic neuroendocrine (islet cell) tumors*. Well-differentiated tumors are often indolent, even in the setting of metastatic disease, and thus, are labeled “cancers in slow motion.”²

Clinical presentation of NETs is commonly in the setting of metastatic disease, resulting from tumor biochemical activity or bulk symptoms. Approximately one-third of pancreatic NETs secrete hormones producing a clinical syndrome; additionally, patients with carcinoid tumors may develop carcinoid syndrome, usually after the development of hepatic metastases.³ Symptoms of hormonal excess from pancreatic NETs and carcinoid tumors are often well controlled with somatostatin analogs, specifically, octreotide and lanreotide.³ Moreover, treatment of well-differentiated tumors with these analogs lengthens time-to-tumor progression (TTP) in randomized controlled trials (RCTs).^{4,5} Newer agents, including sunitinib and everolimus, also improve progression-free survival of pancreatic NETs over placebo in RCTs.^{6,7}

Along with tumor grade, liver metastases are a critical prognostic factor occurring in approximately 40% of patients over the course of their disease.⁸ Systemic chemotherapy has limited success in treating patients with low-grade liver metastatic neuroendocrine tumors (mNETs),

and as such, a variety of local therapy options are employed for controlling symptoms and tumor growth.⁹ Surgical management of liver mNETs remains the only potentially curative option with 5-year survival rates of 60% to 80%; however, only approximately 10% of patients are candidates for curative resection.¹⁰⁻¹² Interestingly, recurrence after surgical management, including the use of intraoperative ablation, is nearly universal, as 94% of patients developed recurrent disease at 5 years in a recent multi-institutional study.¹⁰ Given this high recurrence rate, the true curative role of surgery is debatable.

Transarterial therapy is a potent local therapeutic option for liver mNET, especially for low-grade tumors with hormonal symptoms or tumor progression on long-acting octreotide. These tumors are typically hypervascular with predominant hepatic arterial supply, as compared to the background liver, which is mostly supplied by the portal vein. Therefore, transarterial therapy is concentrated in the tumor, which can greatly limit hepatic and systemic toxicities. Intra-arterial therapy options are transarterial embolization (TAE), transarterial chemoembolization (TACE), and radioembolization (yttrium-90 [Y-90]). These catheter-based therapies demonstrate effectiveness in both tumor control and symptom relief. A case example of each is presented, with review of salient patient selection considerations and outcomes data, followed by a brief discussion of special considerations.

TRANSARTERIAL EMBOLIZATION

Targeted embolization of the hepatic artery, with a variety of particulate embolics, produces tumoral ischemic necrosis while the surrounding liver is perfused by the portal vein (case 1). Treatment is typically followed by an

overnight hospital stay for managing postembolization syndrome (self-limiting pain, fever, and nausea/vomiting).

The use of TAE for treatment of liver mNET is institution-specific, as there is no level 1 evidence guiding patient selection or timing of treatment. It is, however, a recognized treatment option by the National Comprehensive Cancer Network (NCCN).¹³ Contraindications to TAE include > 75% replacement of liver parenchyma with tumor, predominant extrahepatic tumor burden, asymptomatic indolent tumors, and hepatic dysfunction.

A retrospective study utilizing small particle polyvinyl alcohol (PVA) reported symptomatic and morphologic responses to embolization for treatment-refractory unresectable liver mNETs. Eighty-nine percent of patients treated for hormonal symptoms responded to embolization, and all patients treated for pain responded with a cumulative 5-year survival of 54%. Postembolization syndrome occurred in most patients, with an 11% major complication rate. The authors concluded that TAE is a simple and effective treatment for symptomatic liver mNETs.¹⁴

TRANSARTERIAL CHEMOEMBOLIZATION

TACE combines intra-arterial delivery of chemotherapy with particulate embolization. Advantages of this combination include an improved chemotherapy pharmacokinetic profile, with increased intratumoral drug concentration and

dwelling time, as compared to systemic drug administration, together with intratumoral ischemia (case 2).

TACE is performed either as oily emulsion of chemotherapy, together with an embolic material (cTACE), or as a drug-loaded bead, where the chemotherapeutic material is integral to the embolic bead (DEB-TACE).

Patient selection for chemoembolization is guided by opinion without level 1 evidence. Contraindications parallel those mentioned with TAE, and TACE is recognized by the NCCN as a treatment option for liver mNET.¹³

Numerous retrospective reviews detail the performance of adding intra-arterial chemotherapy to hepatic artery embolization (hence cTACE vs TAE). Ruutinen et al demonstrated trends that favor cTACE over TAE, with improvements in TTP, symptom control, and survival; however, this study lacked statistical power to definitely resolve these differences. Notably, the safety profile of the two techniques was similar; therefore, the addition of chemotherapy was not associated with a higher degree of toxicity compared to TAE.¹⁵ A large, multicenter, retrospective, follow-up review compared cTACE to TAE, with the hypothesis that cTACE would result in better symptom control and overall survival than TAE, without increased toxicity. Nevertheless, they

CASE 1

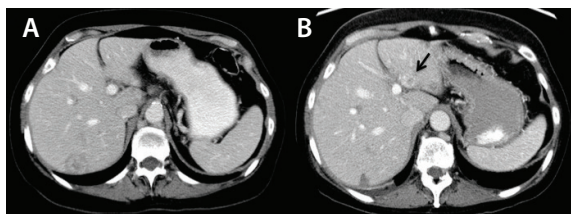


Figure 1. A 58-year-old woman presented with symptomatic unresectable liver metastatic pancreatic NET refractory to octreotide and systemic chemotherapy. Contrast-enhanced CT showed a representative right lobe lesion with a hypervascular rim. The patient was treated with selective right posterior hepatic artery embolization utilizing 100 – 300 micron spherical embolics (A). Contrast-enhanced CT 6 months after embolization shows a marked decrease in the size of the target lesion without enhancement, compatible with a favorable treatment response. A new lesion was identified in the untreated left lobe (arrow) (B). This lesion was subsequently treated with selective embolization. The patient had complete symptom resolution without any adverse events.

CASE 2

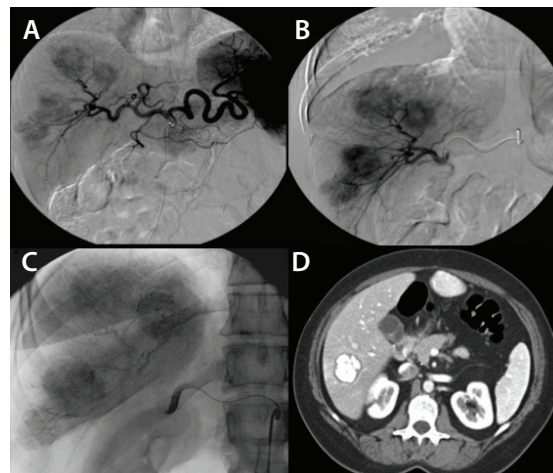


Figure 2. Digital subtracted images from celiac (A) and right hepatic artery (B) angiograms demonstrating multiple hypervascular liver masses in a patient with unresectable NET metastatic to the liver. An unsubtracted right hepatic artery angiogram demonstrating dense accumulation of oil in the tumors after cTACE (C). Postcontrast CT 1 month after cTACE demonstrated homogenous uptake of oil in a representative tumor without viable enhancement (D).

observed no statistically significant difference in the symptom control, overall survival, or toxicity associated with these techniques.¹⁶ Taken together, these results suggest that the addition of chemotherapy to transarterial embolization does not provide a benefit for symptom control or survival, yet this addition does not increase toxicity.

DEB-TACE is an alternative method of chemoembolization, yet data regarding its use for liver mNETs are limited. A prospective study by de Baere et al reported an 80% imaging partial-response rate at 3 months and median TTP of 15 months for low-grade liver mNETs, with symptom control in 81% of patients.¹⁷ These efficacy data compare favorably with TAE and cTACE; however, evidence suggests a higher rate of biliary complications when DEB-TACE is utilized. Guu et al found that DEB-TACE and mNET were independent risk factors for biloma/liver infarct.¹⁸ Additionally, a phase 2 trial was interrupted when 54% of patients treated with DEB-TACE for liver mNET developed a biloma.¹⁹ The increased risk of biliary injury may be secondary to the high local chemotherapy concentrations achieved by DEB-TACE, coupled with the absence of a hypertrophied peribiliary plexus, which is found in cirrhotic livers and is believed to be protective against ischemic and chemical insults.¹⁸

RADIOEMBOLIZATION (Y-90)

Radioembolization delivers high-dose internal radiation to liver tumors via the hepatic artery (case 3). This technique differs from external beam radiation therapy, where hepatic radiosensitivity limits the amount of activity that can be prescribed before the development of radiation-induced liver disease.²⁰

Radioembolization is usually performed with microspheres loaded with Y-90, a beta-emitting isotope.²¹ These microspheres emit high-energy, low-penetration radiation (~2.5 mm) within the tumor. There are two commercially available Y-90 devices: glass-based TheraSphere (BTG Interventional Medicine) and resin-based SIR-Spheres (Sirtex Medical Limited). Despite technical product differences, response rates between devices for liver mNETs appear equivalent.²² In distinction to TACE, hepatic artery occlusion is not intended with radioembolization.²³ Instead, microspheres lodge in the tumor microenvironment and emit lethal beta radiation over an approximate 2-week period.²⁴ The lack of macroscopic vessel occlusion limits postembolization syndrome, and therapy is administered as an outpatient.^{23,25}

Similar to other arterial therapies, Y-90 device selection for treatment of liver mNETs is institution-specific, without level 1 evidence guiding patient selection and timing of treatment. It is, however, a recently recognized treatment option by the NCCN.¹³ Absolute contraindications include significant hepatopulmonary shunting and uncorrectable

hepatoenteric arterial communications, which yield non-target radiation (specifically, radiation pneumonitis and gut ulceration). Notably, portal vein thrombosis is not a contraindication, given the minimally embolic nature of this therapy, as compared to TAE and TACE, thus limiting the risk of ischemic hepatitis.

Y-90 radioembolization is a safe and efficacious therapy for mNETs.²⁶ A recent meta-analysis of resin Y-90 for liver mNETs demonstrated a pooled response rate of 50%, a disease control rate of 86%, and improved overall survival for patients responding to therapy, as compared to non-responders. These rates compare favorably with somatostatin analogs, cytotoxic chemotherapy, and newer biologic therapies.²⁷ A comparative review of Y-90, TAE, and TACE for unresectable liver mNETs was reported by Yang et al. The authors indicate that the aforementioned transarterial therapies showed comparable efficacy in terms of tumor response, symptom palliation, and lengthening patient survival. Distinctions between the techniques occurred in their side effect profiles with no difference in major complication rates.¹²

SPECIAL CONSIDERATIONS

Although the technique for TAE, TACE, and Y-90 is typically unchanged when treating NETs, compared to other primary and secondary liver malignancies, certain disease-specific considerations and complications are either unique or encountered more frequently in this patient population, requiring modification to periprocedural care.

A unique consideration is the potential for carcinoid crisis (a more severe form of carcinoid syndrome that includes profound hypotension or hypertension, confusion, and bronchospasm) resulting from surgical manipulation or general anesthesia. This rare but well-known complication

CASE 3

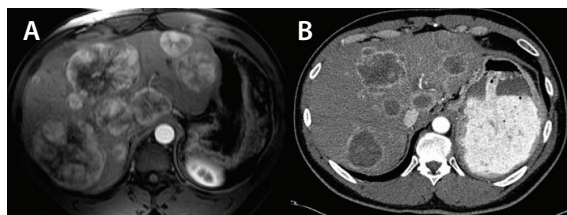


Figure 3. A 63-year-old man presented with bulk symptoms from an unresectable liver mNET tumor. Contrast-enhanced MRI showed bulky bilobar enhancing masses consistent with biopsy-proven carcinoid tumor (A). The patient was treated with sequential lobar Y-90. Three-month posttreatment CT showed decreased size of the bilobar lesions with associated tumor necrosis (B). The patient experienced a durable resolution of bulk symptoms.

can similarly occur during or after transarterial embolization treatment, even in patients not previously demonstrating carcinoid syndrome. In most cases, carcinoid crisis can be prevented by periprocedural administration of short-acting somatostatin analogs.

Although not unique to the treatment of NET, special consideration should be made for patients lacking a competent sphincter of Oddi, often due to previous pancreaticoduodenectomy. Hepatic artery embolization in the setting of a bilioenteric anastomosis is well known to markedly increase the risk of hepatic abscess, ranging from 33% to 86%, despite aggressive antibiotics.^{28,29} Recently, there is evidence that radioembolization, along with antibiotic prophylaxis, may lower this risk. Cholanpranee et al retrospectively reported that zero of 16 patients undergoing radioembolization developed a hepatic abscess, compared to three of 13 patients who underwent cTACE, despite identical periprocedural antibiotic and bowel regimens.³⁰ Additionally, a prolonged course of oral moxifloxacin for 21 days (beginning 3 days before the procedure) without bowel preparation, retrospectively demonstrated no hepatic abscess in 10 patients undergoing 25 embolization procedures.³¹

CONCLUSION

Managing liver mNET is complex and requires a multidisciplinary approach that takes into account the extent and biology of disease. Treatment of liver mNET is undertaken in both curative and palliative settings with the goal of improving survival and quality of life. Catheter-based interventions provide a diverse platform of palliative treatment options, ranging from embolization with resultant tumor ischemia, to intratumoral delivery of high-dose cytotoxic chemotherapy, or lethal internal radiation. These transarterial therapies are effective in controlling tumor burden and related symptoms with a low risk of adverse events. Special considerations include prevention of carcinoid crisis and mitigating risk of postembolization biloma and hepatic abscess. No intra-arterial technique has shown superiority in an RCT, and an evidenced-based treatment algorithm is awaited. In the meantime, a rational approach should recognize catheter-based therapies as a powerful targeted option for liver mNETs. ■

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