Intra-Arterial Liver-Directed Therapies for Neuroendocrine Hepatic Metastases

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Abstract

Keywords

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- interventional radiology

Hepatic metastases, which are frequently seen in patients with neuroendocrine tumors (NETs), have a major adverse impact on the patient's quality of life and survival. Surgery is the treatment of choice for hepatic metastases but is possible in only a small percentage of patients. Systemic chemotherapy yields disappointing results. Somatostatin analogs are effective in controlling symptoms in many of these patients; however, the disease can become refractory to treatment. Transcatheter intra-arterial liver-directed therapies, such as hepatic artery embolization, chemoembolization, and radioembolization are frequently used in patients with NETs metastatic to the liver, especially in patients with refractory, unresectable, or recurrent disease. These treatments are effective in palliating the hormonal symptoms as well as achieving objective tumor responses. This review focuses on the technique, safety, and clinical efficacy of hepatic artery embolization, chemoembolization, and radioembolization in patients with metastatic NETs.

Objectives: Upon completion of this article, the reader will be able to discuss the role of transarterial therapy in the treatment of neuroendocrine liver metastatic disease.

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Neuroendocrine tumors (NETs) include a variety of tumors that have the capacity to synthesize and secrete hormonally active polypeptide products.¹ NETs are slow-growing tumors with a predisposition to metastasize to the liver.² At presentation, 46 to 93% of patients with NETs have hepatic metastases.³ Liver metastases can severely impair a patient's quality

of life and are associated with a poor prognosis, with 5-year survival rates of 0 to 40%.^{1,4}

Treatment options for patients with liver metastases are limited. Patients with neuroendocrine hepatic metastases, especially those experiencing debilitating hormonal symptoms, are treated initially with somatostatin analog therapy.⁵ However, the disease can become increasingly refractory to this treatment. Surgery is the only therapeutic option that offers the possibility of cure for liver metastases. However, only a small percentage of patients (10 to 15% according to various studies) are suitable candidates for curative resection.^{2,5,6} Systemic chemotherapies yield response rates varying between 0% and 38% for patients with metastatic carcinoid tumors.^{7,8} Islet cell neoplasms are generally more responsive to systemic chemotherapy, with reported response rates between 30% and 70% with streptozocin-based chemotherapies.^{4–8}

Transcatheter intra-arterial tumor therapies involve the intravascular delivery of therapeutic agents via selective catheter placement with imaging guidance.⁹ Chemotherapeutic agents, embolic particles, and radioactive materials can be injected via feeding vessels into tumor(s) in an attempt to achieve tumor cell death. Transcatheter intra-arterial

tumor therapies are widely used to treat patients with NETs metastatic to the liver. They are effective in controlling hormonal symptoms and in achieving a durable tumor response.^{10–13} This article reviews the current role of intra-arterial treatment options in patients with liver metastases attributable to NETs.

Indications for Liver-Directed Intra-Arterial Therapies

The presence of hepatic metastatic disease in patients with NETs is associated with poor prognosis, with an established 5-year survival rate of 20 to 25%.^{1,4} An aggressive multidisciplinary treatment approach that includes surgery and locoregional therapies improves survival and quality of life in these patients.¹⁴

Intra-arterial liver-directed therapies are generally used in NET patients with liver-dominant metastatic disease who have symptoms related to hormonal excess or tumor bulk or to those who present with rapid progression of liver disease, especially in patients with refractory, unresectable, or recurrent disease.^{10–13} Liver-directed treatment can occasionally also be used as an adjuvant therapy to reduce tumor load before hepatic resection, hepatic transplantation, or tumor ablation.¹¹

Hepatic Arterial Embolization and Chemoembolization: Technique and Outcomes

NETs that have metastasized to the liver are generally hypervascular and receive between 80% and 90% of their blood supply from the hepatic artery. This feature, combined with the fact that normal liver receives 80% of its blood supply from the portal vein, provides a good rationale for using either hepatic arterial embolization or chemoembolization to treat these metastases. Hepatic artery embolization involves administering embolic agent into the hepatic artery that is supplying the tumors with the goal of inducing tumor ischemia. Hepatic artery chemoembolization combines intra-arterial delivery of chemotherapeutic agents with particulate embolization and combines local cytotoxic effect of chemo-

therapeutic agents with selective ischemia induced by embolization. Slowing of blood flow by embolization also prolongs drug retention in a tumor.

Patient Evaluation/Work-Up

Preprocedure evaluation should include a tissue diagnosis, cross-sectional imaging, history and physical examination, and laboratory evaluation. Laboratory studies include complete blood count, coagulation profile, renal and liver function tests, and relevant tumor markers. Contrast-enhanced computed tomography or magnetic resonance imaging should be performed, ideally within 1 month prior to treatment, to assess volume and distribution of liver disease, presence and extent of extrahepatic disease, and portal vein patency.

Technical Aspects

Initially, diagnostic superior mesenteric and celiac angiography is performed to evaluate the hepatic vasculature (including anatomical variants), vessels supplying the liver tumor(s), and tumor vascularity, and to ensure patency of the portal vein. After diagnostic angiography, embolization or chemoembolization is then performed using a microcatheter placed in a selective location to minimize nontarget embolization. For hepatic artery embolization, the embolic agent of choice is infused through the microcatheter until the selected vessel demonstrates complete or near-complete stasis of flow (►Fig. 1). Commonly used embolic agents for hepatic artery embolization include Gelfoam sponge (Gelfoam, Upjohn, Kalamazoo, MI), polyvinyl alcohol particles (Contour; Boston Scientific, Natick, MA, USA), and tris-acryl gelatin microspheres (Embospheres, Biosphere Medical, Rockland, MA). For chemoembolization, the combination of an embolic agent and the chemotherapeutic drug is administered in a fashion similar to that used for hepatic artery embolization (►Fig. 2).

Embolization technique and extent depend on the number, size, and distribution of liver lesions. Patients with unilobar disease can be treated with lobar embolization or selective catheterization and embolization of individual branches supplying the tumor. In patients with bilobar liver involvement, embolization of the entire liver during a single treatment session is not recommended because of risk of liver

Figure 1 A 60-year-old man with metastatic carcinoid treated with lobar embolization. (A) Computed tomography (CT) scan shows multiple liver lesions involving both lobes of the liver. (B) Superior mesenteric angiogram shows replaced common hepatic artery with multiple hypervascular liver tumors. The patient was treated with right and left hepatic artery bland embolization in two treatment sessions, separated by a 4-week interval. (C) Follow-up CT scan shows decrease in number and size of liver tumors.

Figure 2 A 45-year-old man with metastatic insulinoma presenting with persistent hypoglycemia. (A) Computed tomography (CT) scan shows a large lesion in segment 7. There were three other liver lesions in the right liver (not shown). (B) Selective right hepatic arteriogram shows multiple hypervascular liver lesions. Chemoembolization was performed using 5-fluoruracil, doxorubicin, and streptozocin mixed with 300 to 500 polyvinyl alcohol particles. (C) Postembolization angiogram shows stasis in right hepatic artery. (D) Posttreatment follow-up CT scan shows tumor necrosis and lack of vascularity within the tumor.

failure.^{12,13} The lobe with the largest tumor burden is typically treated first. In the case of extensive bilobar disease with >75% liver involvement, embolization procedures can be staged, and different liver segments may be embolized at each treatment session.^{10–13} The timing of subsequent embolizations is determined primarily by a patient's tumor burden and his or her ability to tolerate the procedure.^{12,13} Depending on the extent of liver involvement, the entire liver can usually be treated in two to four sessions. Although there is no absolute contraindication to embolization or chemoembolization, complete portal vein occlusion, poor performance status, and hepatic insufficiency are considered relative contraindications to these treatments.^{15,16} Embolization should not be performed in patients with bilirubin levels >2 to 3 mg/dL. Patients who have undergone previous biliary-enteric anastomoses are at very high risk for developing a liver abscess after chemoembolization, even when standard prophylactic antibiotic therapy is used.¹⁷ A few recent reports suggest that use of aggressive antibiotic prophylaxis with bowel preparation may protect against hepatic abscesses after chemoembolization in such patients.¹⁷ Geschwind et al described no abscesses in a group of four patients who received intravenous (IV) tazobactam/piperacillin along with bowel preparation before treatment.¹⁸ Similarly, Patel and others used long-term antibiotic prophylaxis and bowel

preparation; they reported a trend toward a lower rate of abscess formation among patients who received more aggressive antibiotic prophylaxis compared with those who received standard prophylaxis.¹⁹ At our institution, patients with biliary-enteric anastomoses undergoing embolization or chemoembolization are treated with the following regimen¹⁹: oral levofloxacin 500 mg daily and metronidazole 500 mg twice daily 2 days before chemoembolization and continued for 2 weeks after discharge, along with bowel preparation with neomycin 1 g plus erythromycin base 1 g orally at 1 PM, 2 PM, and 11 PM the day before chemoembolization. In a more recent study, Khan et al showed that prophylactic treatment with moxifloxacin alone was successful in preventing liver abscess in 10 patients treated with 25 embolization or chemoembolization procedures, avoiding the need for bowel preparation.²⁰

Some reports have suggested that embolization and chemoembolization should not be performed in patients with a tumor burden involving >50% of the liver because of the high risk of inducing liver failure. Carrasco and associates reported a high mortality rate for patients with >50% liver involvement by metastatic disease.^{21,22} In another report by Kress and colleagues,²³ most of the patients with a tumor burden >75% died 30 days to 6 months after undergoing chemoembolization as a result of liver failure or tumor progression. However,

results of a study from MD Anderson Cancer Center suggest that, although response rates and survival durations are lower in patients with >75% liver involvement than in those with lesser liver involvement, many of these patients can be safely treated and can even benefit from this treatment if only small portions of the liver are embolized during each session.^{12,15} In a 2008 study of patients with hepatic NET metastases and liver involvement >75% who were treated at the author institution with selective segmental sequential embolization or chemoembolization, radiologic response or disease stabilization was seen in 82% of patients; symptomatic response was seen in 65% of patients; and the median progression-free and overall survival durations were 9.2 months and 17.9 months, respectively.¹⁵ However, this 2008 study also indicated that embolization or chemoembolization can be associated with a high risk for procedure-related mortality in patients with massive liver tumor burden if they have additional risk factors such as carcinoid heart disease, sepsis, rapidly worsening performance status, or anasarca.¹⁵

The therapeutic benefit of chemoembolization over bland embolization for this patient population remains unclear. A review of various published studies suggests that no difference in response rates exists between these treatment methods.^{12–14,23–50} Several different chemotherapeutic agents have been used in various studies, and there is no consensus on which chemotherapeutic agent to use. Most commonly used drugs for chemoembolization include doxorubicin and streptozocin, alone or in combination with cisplatin, 5-fluorouracil, and mitomycin-C. Results of the author experience at MD Anderson reveal that although chemoembolization did not demonstrate a therapeutic advantage over bland embolization in patients with carcinoid tumors, patients with islet cell carcinoma treated with chemoembolization had a tendency toward a more prolonged survival (31.5 months versus 18.2 months) and a better radiologic response rate (50% versus 25%) than did those treated with embolization alone; however, these differences did not reach statistical significance.¹² This was not an unexpected result because carcinoid tumors are known to be more resistant to systemic chemotherapy than are islet cell carcinomas. In another retrospective multi-institutional review comparing chemoembolization and bland embolization, patients treated with chemoembolization demonstrated a trend toward improved time to progression, symptom control, and overall survival.⁴¹ Again, statistical significance was not achieved because of the small cohort, warranting the necessity for further prospective randomized trials. At MD Anderson, patients with metastatic carcinoid tumors are treated with bland embolization; those with metastatic islet cell tumors are treated with chemoembolization. There is marked variability in the chemoembolization protocol based on institutional and operator preferences. Some mix the chemotherapy with particulate agents, some infuse the chemotherapy initially followed by embolization with particles, some emulsify the chemotherapy with lipiodol, and others use the sandwich technique that involves particle embolization before and after chemotherapy infusion. Literature review shows there is no difference in the outcomes between the various techniques,

and there are no data supporting superiority of any one chemoembolization regimen over the others.

Outcomes

Many nonrandomized retrospective reports have shown that embolization and chemoembolization can reduce hormone levels, palliate symptoms, and reduce tumor burden in patients with NET hepatic metastases.^{12–14,23–50} A review of the literature shows that embolization and chemoembolization can result in imaging response in 25 to 95% of patients and symptomatic response in 50 to 100% of patients with NET liver metastasis (►Table 1). Reported 5-year survival rates vary between 13.7% and 83%.^{12–14,23–50} This wide range in response rates and survival durations is a reflection of the marked heterogeneity in the reported studies in terms of patient demographics; extent of liver involvement by metastatic disease; presence or absence of extrahepatic disease; tumor histology and degree of differentiation; treatment regimens used (bland embolization versus chemoembolization, number of embolization sessions, choice and/or dose of the chemotherapeutic drug and embolic agent); the time when embolization was performed (i.e., early or late in the clinical course); concurrent use of octreotide and systemic chemotherapy; frequency and timing of follow-up imaging; criteria used to evaluate response; and methods used to report survival.

In keeping with the results reported in the medical and surgical oncology literature, patients with carcinoid tumors treated with embolization or chemoembolization experience better outcomes than do those with islet cell tumors treated in a similar fashion (►Table 1). Eriksson et al reported the median survival duration in patients with carcinoid tumors at 80 months, but only 20 months in patients with islet cell tumors.³¹ Moertel and colleagues reported a longer median survival (27 months versus 9 months) in patients with carcinoid tumors treated with liver embolization or surgical ligation of the hepatic artery than in those with islet cell tumors.³⁶ A study from MD Anderson showed that patients with carcinoid tumors had significantly higher radiologic response rates (66.7% versus 35.2%; $p = 0.0001$) and longer median progression-free survival (22.7 months versus 16.1 months; $p = 0.046$) and overall survival durations (33.8 months versus 23.2 months; $p = 0.012$) than did patients with islet cell tumors.¹²

Although many studies have reported on the use of embolization or chemoembolization in patients with metastatic NETs, several unresolved issues remain. There is, however, a lack of consensus among interventional radiologists regarding the ideal chemoembolic regimen, procedure end points, the degree of vascular stasis to be achieved, and the ideal time interval between treatment sessions. In addition, because of the lack of randomized controlled trials, unequivocal survival benefit has not yet been established. In a 2011 study with long-term follow-up (mean follow-up: 3.2 years; range: 2 weeks to 18.3 years), Dong and Carr found that the overall 3-, 5-, and 10-year patient survivals were 59%, 36%, and 20%, respectively, with a mean patient survival of 3.3 years.⁵⁰ These authors concluded that chemoembolization for

Table 1 Literature findings on Hepatic Arterial Embolization and Chemoembolization for Treatment of Metastatic Neuroendocrine Tumors

Study	Tumor type	N	EHD (%)	Treatment	Imaging response (%)			Symptom response (%)	Tumor marker response (%)	Median TTP/PFS (mo)	Median survival ^a (mo)	5-y survival ^a (%)
					CR plus PR	SD	PD					
Ajani et al ²⁴	Islet cell	22	NR	TAE	60			NR	NR	NR	33.7	NR
Hanssen et al ²⁵	Carcinoid	36	NR	TAE	60	20	20	100	NR	NR	NR	75
Ruszniewski et al ⁴⁰	Carcinoid	18	NR	TACE (dox)	33			73	57	NR	NR	NR
	Islet cell	5	NR	TACE (dox)		60		NR		NR	NR	NR
Therasse et al ⁴³	Carcinoid	23	NR	TACE ^b	33	50	11	100	91	NR	24	NR
Perry et al ³⁸	NET	30	NR	TACE (dox)	95			90	69	NR	24	NR
Wangberg ⁴⁵	Carcinoid	40	NR	TAE	42.5	37.5		NR	100	NR	NR	63
Eriksson et al ³¹	Carcinoid	29	NR	TAE	52	31		NR	38	NR	80	60
	Islet cell	12	NR		50	8		NR	42	NR	20	NR
Diamandidou et al ²⁸	NET	20	NR	TACE (cis)	33.3	66.6		67	73	NR	NR	NR
Brown et al ²⁷	NET	35	NR	TAE				96	NR	NR	NR	54
Kim et al ⁴⁷	Carcinoid	16	NR	TACE (cis/dox)	25			NR	75	NR		NR
	Islet cell	14	NR	TACE (STZ/5-FU)	50			NR	90	NR		NR
Chamberlain et al ¹⁴	NET	33	45	TAE				96	NR	NR	NR	51
Yao et al ⁴⁶	NET	20	NR	TACE (dox/cis/mit-C)	25	10		50	NR	NR	32	40
Roche et al ³⁹	NET	14	7.1	TACE (dox)	43			90	NR	NR	NR	83 ^c
Loewe et al ³⁴	Carcinoid	23	≥48	TAE	73	22		NR	61.5		69	65.4
Kress et al ²³	NET	26		TACE (dox)	7.7	53.8	19.2	NR	NR	NR	NR	48 ^c
Gupta et al ¹²	Carcinoid	69	70	TAE or TACE ^b	66.7	24.6	8.7	NR	NR	22.7	33.8	26.6
	Islet cell	54	57		35.2	61.1	3.7	NR	NR	16.1	23.2	13.7
Osborne et al ³⁷	NET	59		TAE				91	NR	NR	24 ^d	NR
Strosberg et al ⁴²	NET	84	26	TAE	48	52		80	NR	36	NR	NR
Varker et al ⁴⁴	Carcinoid	122	NR	1st TACE (cis/dox/mit-C)	82			92	NR	11.8	33.3	NR
	Carcinoid	27	NR	Repeat TACE (cis/dox/mit-C)	61			77	NR	NR	28.1	NR
Bloomston et al ²⁶	Carcinoid	122	28	TACE ^b	82	12	6	92	80	NR	33.3	NR
Ruutinen et al ⁴¹	NET	67	NR	TAE	50	38	13	93	NR	6	39	33
			NR	TACE (cis/dox/mit-C)	66	22	12	92	NR	12	44	50
Ho et al ³³	Carcinoid	31	NR	TAE or TACE (cis/dox/mit-C)	23	32	23	78	NR	22.7 ^d	41.8 ^d	32
	Islet cell	15	NR		18	45	9	75	NR	16.1 ^d	43.7 ^d	35
de Baere et al ⁴⁸	NET	8	60	TACE (DEB/dox)	80	15	1	NR	NR	15	NR	NR
Dong and Carr ⁵⁰	NET	123	NR	TACE ^b	62	24	14	NR	NR	NR	65	36

Abbreviations: chemo, chemotherapy; cis, cisplatin; CR, complete response; dox, doxorubicin; EHD, extrahepatic disease; 5-FU, 5-fluorouracil; IV, intravenous; mit-C, mitomycin-C; NET, neuroendocrine tumor; NR, not recorded; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; STZ, streptozocin; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization; TTP, time to progression; vinb, vinblastine; DEB, drug-eluting beads.

^aFrom the date of TAE/TACE.

^bMultiple chemotherapeutic regimens.

^cFrom diagnosis.

^dMean.

unresectable NETs metastatic to the liver is associated with prolonged survival. The time at which embolization treatment should be performed, whether early or late in the course of disease, also remains unclear. Although some investigators advocate early embolization, others suggest late embolization can be equally effective. Hanssen and colleagues, who observed a higher response rate in patients with carcinoid tumors treated at the time of diagnosis with embolization followed by interferon therapy than the response in patients who received interferon only (86% versus 42%), concluded that embolization should be performed early in the course of disease.²⁵ However, Erickson and associates performed embolization or chemoembolization at a median of 37 months after diagnosis and observed a median survival of 80 months and a 5-year survival rate of 60%, indicating that relatively late embolization also is effective.³¹ These findings complement the author's experience at MD Anderson; the duration of liver disease before embolization did not influence response rates or survival durations after embolization or chemoembolization.¹²

In recent years, drug-eluting beads have been used to administer chemoembolization as a means to deliver a more accurate dose of anticancer drugs to liver tumors over a prolonged period. Drug-eluting beads are biocompatible, hydrophilic, nonresorbable hydrogel microspheres that are available in various sizes. These beads can be loaded with chemotherapeutic medications, which then release in a controlled and sustained fashion. However, data on the use of chemoembolization using drug-eluting beads in patients with NETs are limited. De Baere et al used doxorubicin-eluting beads (500 to 700 μm) in 20 patients with progressive liver metastases resulting from NETs.⁴⁸ Partial response (PR) and stable disease (SD) were noted in 16 (80%) and 3 (15%) patients, respectively. At 15-month follow-up, nine patients (45%) maintained SD. These authors concluded that chemoembolization with drug-eluting beads is safe and effective. In another study, Gaur and associates performed 38 drug-eluting bead (100- to 300- μm or 300- to 500- μm beads preloaded with 50 to 100 mg doxorubicin) chemoembolization procedures in 18 patients with NETs metastatic to the liver.⁴⁹ At short-term follow-up (<3 months), 22 of 38 procedures (58%) produced a radiologic response, with the remainder having SD. At intermediate-term follow-up (mean: 445 days; range: 163 to 1247 days), 17 of 26 procedures (65%) produced a radiologic response. However, at present, there is no evidence in the published literature to suggest that drug-eluting beads offer any therapeutic advantage over bland embolization or conventional chemoembolization in patients with metastatic NETs.

Complications

Postembolization syndrome, characterized by right-upper-quadrant pain, fever, nausea, leukocytosis, and elevated liver function test findings, is seen most patients after embolization or chemoembolization; this syndrome is generally self-limited and improves within 3 to 5 days, but occasionally it is severe and requires prolonged hospitalization.^{12,15} Complications such as carcinoid crisis, acute liver failure, hepatic

encephalopathy, emphysematous cholecystitis, gastric ulcer and hemorrhage, abscess formation, and tumor lysis syndrome are uncommon.^{12,14,15} Hepatic artery embolization in patients with functional carcinoid metastases can occasionally precipitate massive acute release of serotonin and other vasoactive peptides resulting in a carcinoid crisis. Carcinoid crisis is a potentially life-threatening event characterized by hypotension or hypertension, arrhythmias, bronchospasm, facial flushing, edema, and metabolic acidosis. Carcinoid crisis is treated by IV administration of 200 μg IV octreotide, repeated as needed until the symptoms are controlled. Octreotide may also be useful in preventing a carcinoid crisis, and its prophylactic administration is recommended prior to any hepatic artery intervention in patients with metastatic carcinoid tumors.

Yttrium-90 Microsphere Radioembolization

Intra-arterial radioembolization with yttrium-90 (⁹⁰Y) microspheres is increasingly being used in patients with unresectable primary and metastatic liver tumors.^{48–50} ⁹⁰Y is a β emitter with a mean soft tissue penetration of 2.5 mm. The two ⁹⁰Y microsphere products approved by the Food and Drug Administration in clinical use are the glass-based TheraSphere (Nordion Inc., Ottawa, Ontario, Canada) and the resin-based SIR-Spheres (Sirtex Medical Ltd., Sydney, New South Wales, Australia). Particle sizes vary between 20 μm and 40 μm . Hepatic arterial administration of the ⁹⁰Y microspheres results in preferential deposition of the microspheres into the tumoral and peritumoral vasculature, allowing the delivery of high doses of radiation to the tumor with relative sparing of the normal liver parenchyma.^{51,52}

Technique

Radioembolization is generally performed in two steps. Diagnostic angiography is performed initially to evaluate the hepatic arterial anatomy and to determine the pulmonary shunt fraction via technetium-99 macroaggregated albumin infusion.^{51–53} Excessive pulmonary parenchymal deposition of the ⁹⁰Y microspheres via pulmonary shunting could result in radiation pneumonitis, which can be avoided by keeping the lung exposure <30 Gy. To avoid nontarget delivery of radioactive microspheres to organs such as the stomach, duodenum, and pancreas, it is essential to perform an angiogram with selective embolization of all extrahepatic arteries before treatment with ⁹⁰Y microspheres (► Fig. 3).

In 2012, Mahvash and colleagues reported an alternative method to prevent nontarget gastrointestinal deposition of ⁹⁰Y microspheres; the technique involves the use of a balloon catheter to temporarily occlude the common hepatic artery to reverse hepatocentric flow for lobar administration of microspheres.⁵⁴ However, the technique should not be used in patients with a significant tortuosity of the common hepatic artery or in patients with anatomical variants, such as the left hepatic artery arising from the gastrohepatic trunk or a replaced right hepatic artery. At MD Anderson, whenever feasible, the balloon occlusion technique is used for ⁹⁰Y radioembolization. The second step involves the delivery of the

Figure 3 A 62-year-old female patient with metastatic islet cell carcinoma treated with radioembolization. (A) Computed tomography (CT) scan shows multiple right liver lesions. Imaging showed left liver lesions as well (not shown). (B) Celiac arteriogram shows multiple hypervascular liver lesions. (C) Selective left hepatic arteriogram shows an aberrant umbilical artery (arrows) arising from the left hepatic artery. (D) This branch (arrows) was selectively catheterized and embolized with coils. (E) Right gastric artery was also embolized with coils (arrow) through a microcatheter placed in the left gastric artery. (F) Celiac arteriogram shows successful coil embolization of the umbilical (arrow) and right gastric (arrowhead) arteries. The patient was treated with whole-liver infusion of ^{90}Y microspheres. (G) Follow-up imaging shows necrosis of liver lesions.

radioactive microspheres. Sequential unilobar or whole-liver treatments can be performed depending on the extent of liver involvement, liver function, variant hepatic arterial anatomy, and institutional and operator preferences. For sequential unilobar infusions, a 4- to 6-week interval between infusions is recommended to allow for resolution of any treatment-related toxicities. For whole-liver infusion, the catheter can be positioned in the proper hepatic artery for infusion of ^{90}Y microspheres. Alternatively, the whole liver can be treated in one session by selective catheterization and infusion in one, followed by the other hepatic artery. Device-specific dosimetry calculations have been discussed in detail in many previous reports and are not included in this article.^{51–53} Periprocedural management in patients undergoing radioembolization involves the use of a proton pump inhibitor or histamine-2 blocker to prevent gastrointestinal injury, antiemetics for

posttreatment nausea, and a short-acting somatostatin analog in patients with functional carcinoid tumors. Although prophylactic antibiotics are not routinely used, aggressive antibiotic prophylaxis is recommended in patients with biliary-enteric anastomoses. Although portal vein thrombosis is considered a relative contraindication for embolization or chemoembolization, it is not necessarily a contraindication for radioembolization. TheraSpheres, because of their lower embolic potential, are the preferred microspheres by some authors for this patient population.^{51–53}

Outcomes

Several studies have reported the results of radioembolization in patients with neuroendocrine liver metastases (►Table 2).^{52,55–61} In a study involving 148 patients with NET liver metastases treated with 185 radioembolization

Table 2 Literature findings on Radioembolization for Treatment of Metastatic Neuroendocrine Tumors

Study	Line	N	Tumor type	EHD (%)	Treatment agent	Imaging/tumor marker response (%)			Symptom response (%)	Median TTP	Median survival
						CR plus PR	SD	PD			
Kennedy et al ⁵⁵	First to salvage	148	82% carcinoid; 18% other NETs	NR	SIR-Spheres	63.2	22.7	4.9	NR	NR	70 mo
King et al ⁵⁷	First or second line or more	34	68% carcinoid; 32% other NETs	59	SIR-Spheres plus 5-FU infusion	50	14.7	32.4	55	NR	24.2 mo
Murthy et al ⁵²	Salvage ^a	8	75% islet cell; 25% carcinoid	62.5	SIR-Spheres	12	50	37.5	NR	NR	14 mo
Rheee et al ⁵⁸	NR	27	67% carcinoid; 33% islet cell	NR	SIR-Spheres or Therasphere	93.8 ^b			NR	NR	18 mo
Kalinowski et al ⁵⁹	NR	9	NR	NR	SIR-Spheres	66.7	33.3		NR	11.1 mo	3 y: 57%
Saxena et al ⁶¹	First to salvage	48	71% carcinoid; 29% other NETs	48	SIR-Spheres	54	23	23	NR	NR	35 mo
Memon et al ⁶⁰	First to salvage	40	82% carcinoid; 18% other NETs	35	Therasphere	64	NR	NR	84	NR	34.4 mo

Abbreviations: CR, complete response; EHD, extrahepatic disease; 5-FU, 5-fluorouracil; NETs, neuroendocrine tumors; NR, not recorded; PD, progressive disease; PR, partial response; SD, stable disease; TTP, time to progression.

^aAll failed previous transcatheter arterial embolization/transcatheter arterial chemoembolization.

^bPR plus SD.

procedures using resin ^{90}Y microspheres, Kennedy et al reported a complete response in 2.7% of patients, PR in 60.5%, SD in 22.7%, and progressive disease in 4.9%.⁵⁵ The median survival was 70 months. In another prospective study that involved nine patients with unresectable liver metastases from NETs treated with ^{90}Y radioembolization, PR was seen in six patients (66%), and survival rates were 100% and 57% for 1 and 3 years, respectively.⁵⁹ No major complications occurred. In a 2012 single-center study involving 40 patients with metastatic NETs treated with ^{90}Y radioembolization, Memon and colleagues reported that the 1-, 2-, and 3-year overall survival rates were 72.5%, 62.5%, and 45%, respectively; overall median survival was 34.4 months.⁶⁰ In a separate study involving radioembolization in 48 patients with unresectable metastatic NETs, Saxena and associates reported a complete or partial response in 54% of patients; the median survival was 35 months.⁶¹ These authors also evaluated the prognostic variables that influenced survival in patients with unresectable metastatic NETs and noted that low hepatic tumor burden ($p = 0.022$), female gender ($p = 0.022$), well-differentiated tumor ($p = 0.001$), and absence of extrahepatic metastasis ($p < 0.001$) were associated with an improved survival.⁶¹ In a retrospective analysis involving eight patients with metastatic NETs, Murthy et al showed that ^{90}Y radioembolization can be safely performed even after previous embolization or chemoembolization, with a median survival time of 14 months after radioembolization.⁵² These results suggest that ^{90}Y radioembolization represents a viable alternative therapy for patients with hepatic NETs, especially those patients in whom traditional therapies have failed. Further investigation, long-term follow-up, and prospective clinical trials are warranted to determine the exact role of this treatment method in the management of NET hepatic metastases.

Complications

The acute and subacute toxicities associated with radioembolization are less severe and better tolerated than those toxicities associated with conventional hepatic embolization procedures. This better toxicity profile, combined with the lower incidence of postembolization syndrome associated with radioembolization, allows for treatment in an outpatient setting.^{51–53} Complications including radiation gastritis, radiation pneumonitis, duodenal ulcers, and liver dysfunction have been reported. Radiation-induced liver disease is rare; the estimated incidence for all tumor types is $<1\%$.⁶²

Hepatic Arterial Infusion of Radiolabeled Somatostatin Analogs

Radiolabeled somatostatin analog imaging has been used to diagnose, localize, and monitor NET treatment response. Octreotide, octreotate, and lanreotide peptides have been used, and all have been modified with the addition of the metal chelator tetraazacyclododecanetetraacetic acid (DOTA).¹⁶ More recently, intra-arterial delivery of these somatostatin analogs labeled with therapeutic radioactive agents has been used to treat liver metastases from NETs. The

commonly used radionuclides include ^{90}Y , indium-111 (^{111}In), and lutetium-177. A diagnostic ^{111}In -pentetreotide scan is performed to assess receptor positivity and to determine whether a patient may benefit from treatment with radiolabeled somatostatin analogs; almost 90% of all carcinoid tumors are receptor positive. However, this percentage can drop to 50% in NETs of pancreatic origin, especially insulinomas.^{16,62} Patients for whom receptor activity at known tumor sites is more intense than activity in a healthy liver are likely to benefit from this treatment,^{63,64} and intra-arterial administration of these radiolabeled somatostatin analogs has been shown to result in modest treatment responses.^{63,64} McStay et al treated 23 patients with NET hepatic metastases with hepatic arterial infusion of ^{90}Y -DOTA-lanreotide and observed a response rate of 16% and 1-year survival rate of 63%.⁶⁵ Limouris and associates, in their series of 17 patients treated with hepatic arterial infusion of ^{111}In -DTPA-D-Phe¹-octreotide, observed a complete or partial response in 53% of patients and a survival of 32 months in 70.5% of patients.⁶⁶

Hepatic Arterial Infusion of Chemotherapy

Hepatic arterial infusion of chemotherapeutic agents permits delivery of relatively higher doses of chemotherapy than systemic administration. There is very limited literature on the use of hepatic arterial infusion chemotherapy in patients with metastatic NETs. Takeuchi and colleagues achieved a PR that was maintained for 40 months in a patient with metastatic carcinoid tumor treated with 40 cycles of intra-arterial methotrexate and fluorouracil (5-FU).⁶⁷ Christante et al treated 77 patients with NET hepatic metastases with four cycles of hepatic arterial infusion of 5-FU.⁶⁸ The last two infusion cycles were combined with chemoembolization using cisplatin, doxorubicin, and mitomycin-C mixed with lipiodol. The authors reported a response rate of 80%, a median progression-free survival duration of 19 months, and a 5-year survival rate of 27%.⁶⁸ At MD Anderson, hepatic arterial infusion chemotherapy is generally reserved for patients in whom embolization or radioembolization is not considered safe because of extensive tumor burden, hepatic insufficiency, or complete portal vein occlusion.

Conclusions

Transcatheter intra-arterial tumor therapies such as hepatic artery embolization, chemoembolization, and radioembolization reduce hormone levels, provide symptom relief, and reduce tumor burden in many patients with unresectable and symptomatic NET hepatic metastases. In selected patients, the use of liver-directed therapies can result in cytoreduction, allowing for potential resection or ablation. In the absence of large-scale controlled trials, it is not possible to draw any conclusion regarding the superiority of one intra-arterial therapy over the other. Treatment selection in individual patient should be based on the disease burden, presence and extent of extrahepatic disease, presence and severity of symptoms, performance status, anatomical factors, and

quality-of-life considerations. Prospective clinical trials comparing the relative safety and efficacy of different treatment options are warranted.

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