Role of Interventional Radiology in the Treatment of Patients with Neuroendocrine Metastases in the Liver

Larry K. Kvols, MD; Kiran K. Turaga, MD, MPH; Jonathan Strosberg, MD; and Junsung Choi, MD; *Tampa, Florida*

Key Words

Neuroendocrine carcinomas, carcinoid tumors, liver metastases, hepatic artery embolization, chemoembolization, radiofrequency ablation

Abstract

Management of liver metastasis from neuroendocrine tumors routinely includes an interventional radiologist. Hepatic artery embolization, either bland (transarterial embolization) or with chemotherapy (transarterial chemoembolization), has been shown to improve response rates in neuroendocrine metastases to the liver. Radiofrequency ablation, cryotherapy, and percutaneous alcohol ablation are important adjuncts or alternative treatments to surgical debulking. In this article, the authors examine important techniques in the armamentarium of the interventional radiologist. (*JNCCN* 2009;7:765–772)

The liver is the predominant site of metastatic disease in gastrointestinal neuroendocrine tumors. In the early 1980s, hepatic artery ligation was recommended for management of patients with symptomatic carcinoid syndrome.¹ In fact, early studies by Moertel et al.¹ showed objective regressions in 60% of patients with metastatic carcinoid to the liver using occlusion alone versus 80%

with chemotherapy added (alternating doxorubicin plus dacarbazine and streptozocin plus fluorouracil).¹ Over the ensuing decades, selective lobar hepatic artery embolization or chemoembolization was found to be significantly more tolerable than surgical ligation.^{2,3} Several ablative techniques were also developed over the past 2 decades, causing interventional radiologists to become important members of the multidisciplinary team managing patients with neuroendocrine tumors. These developments are reflected in the current guidelines of the NCCN, which list both embolization and ablative techniques for managing patients with metastatic neuroendocrine tumors (Table 1).⁴

Hepatic Artery Embolization

Although surgery remains the preferred procedure for patients with localized hepatic metastasis, it is rarely an option (10%–20%) for those with disseminated or multifocal disease.^{5–7} Although liver transplantation has been reported in sporadic series for multifocal metastatic neuroendocrine tumors, the lack of donor livers and variable survival rate (36%–87%)^{6,8,9} reported make it a nonviable option for most patients. The rationale for hepatic artery embolization is based on the observation that these hypervascular tumors derive most of their blood supply from the hepatic artery.^{5,10} Moreover, hepatic metastases are known to compress adjacent portal sinusoids, which are the primary blood supply sites for normal liver tissue. In patients with progressive or symptomatic metastases predominantly confined to the liver, embolization or chemoembolization of the hepatic artery can be recommended as first-line therapy.

Typically, each lobe of the liver is embolized selectively.

From the H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida.

Submitted February 2, 2009; accepted for publication April 28, 2009.

Dr. Kvols has disclosed that he is a consultant for and on the advisory board and speakers' bureau for Novartis Pharmaceuticals Corporation (compensation totals more than \$10,000). Drs. Turaga, Strosberg, and Choi have disclosed that they have no interests, arrangements, or affiliations with the manufacturers of any products discussed in the article or their competitors.

Correspondence: Larry K. Kvols, MD, Neuroendocrine Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL 33612. E-mail: larry.kvols@moffitt.org

Table 1 Summary of First-Line Management for Metastatic Neuroendocrine Tumors*

Type of Metastatic Neuroendocrine Tumor	First-Line Therapy in Asymptomatic Patients	First-Line Therapy in Symptomatic Patients
Carcinoid: foregut (esophagus, stomach, bronchial)	Surgery if possible Observation	Somatostatin analogues Surgery if possible <i>RFA/alcohol ablation/cryoablation</i>
Midgut (small intestine, colon)	Surgery if possible Observation	Somatostatin analogues Surgery if possible <i>RFA/alcohol ablation/cryoablation</i> <i>Chemoembolization</i> (if advanced or progressive disease)
Hindgut (colon, rectum)	Surgery if possible Observation	Somatostatin analogues Surgery if possible <i>RFA/alcohol ablation/cryoablation</i>
Noncarcinoid tumors (Islet cell tumors): gastrinoma, insulinoma, vipoma	Surgery if possible Observation	Somatostatin analogues Surgery if possible <i>RFA/alcohol ablation/cryoablation</i> <i>Chemoembolization</i> (if advanced or progressive disease) Chemotherapy

*Based on the NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors, Version 1, 2009, highlighting the role of interventional radiology (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).
Abbreviation: RFA, radiofrequency ablation.

Thus, the entire liver can be treated in 2 to 3 stages, depending on the extent of disease. Chemotherapeutic agents are often added to the embolic material (doxorubicin, streptozocin); however, whether addition of chemotherapy improves outcomes is still uncertain.

Embolization Procedure

A diagnostic celiac angiogram is performed to identify the hepatic vasculature, patency of the portal vein, and number and location of hepatic metastases. Presence of portal vein occlusion and ascites are considered relative contraindications for the procedure. A superior mesenteric arteriogram is performed in the presence of a replaced or accessory hepatic artery. Subcutaneous octreotide is often administered immediately before the procedure in patients with the carcinoid syndrome to prevent acute release of serotonin into the circulation. Subselective catheterization of the right or left hepatic artery is performed using an angled 5 Fr catheter or 3 Fr microcatheter coaxially through the 5 Fr angled catheter placed in the origin of the celiac artery or superior mesenteric artery.

Embolization is performed under fluoroscopy. Various particulate materials have been used, including 250- to 355- μ m diameter polyvinyl alcohol particles and 500- to 700- μ m diameter microspheres. For chemoembolization, an emulsion of a cytotoxic drug such as doxorubicin, mitomycin C, or cisplatin, or a combination of these, is dissolved in 10 mL of normal

saline (0.9%) combined with 10 mL of iodized oil, which is injected into the subselected right or left hepatic artery. The embolization procedure is performed until near complete stasis of flow. Usually the liver lobe with the bulkiest disease is embolized first. Antiemetics and adequate analgesia should be provided, and preoperative intravenous hydration is important. Perioperative antibiotics should be administered (e.g., levofloxacin and flagyl) for at least 72 hours to prevent abscess formation. Individual embolizations are spaced 4 weeks apart, and most patients complete their embolizations in 2 or 3 stages.¹¹ Follow-up imaging studies are typically performed 1 to 2 months after the last embolization.

Minor complications are common, such as transient nausea, vomiting (50%–70%), abdominal pain (50%–60%), and fevers (30%–60%).¹¹ Hepatic transaminases typically increase, peaking 2 to 3 days after each embolization.¹¹ Most side effects resolve within 1 week. Acute hypertension is occasionally observed in patients with carcinoid syndrome during or immediately after the embolization procedure. Elevated liver enzymes are also seen (100% peak usually within 2–3 days). Severe complications, such as gastric perforation, gastritis, bleeding peptic ulcers, and duodenitis, can usually be avoided with highly selective catheterization. Hepatic and renal failure has also been reported after repeated embolization treatments.¹²

Response Rates

Hepatic arterial embolization has been shown to provide symptomatic relief in 59% to 100% of cases (Table 2). Symptomatic responses occur as a result of reduction in hepatic tumor burden and decrease of hormonal output in functional tumors.^{13–16} For example, major decreases in 5-hydroxyindoleacetic acid (5-HIAA) levels (> 50% reduction) occur in 51% to 91% of patients with carcinoid syndrome.^{16–20}

Objective tumor responses have been noted in 33% to 80% of patients (Table 3). This is a heteroge-

neous rate caused by variation in the type of tumors, choice of cytotoxic agent, and concomitant use of somatostatin analogues. The extent of liver involvement has been proposed to be predictive of tumor response.¹⁸

Novel Strategies in Hepatic Artery Embolization

Radioembolization using yttrium 90 as a source of beta energy is currently approved in the United States for the treatment of hepatocellular and colorectal cancers. Yttrium 90 is a pure beta emitter that decays over a half-life of 64.2 hours. During manufacturing, yttrium 89 is incorporated into a stable glass matrix or

Table 2 Symptomatic Response in Patients With Metastatic Neuroendocrine Tumors Treated With Transarterial Chemoembolization

Author	Year	Number of Patients	Tumor Type	Chemotherapy	Symptomatic Response % (in Symptomatic Patients)	Biomarker Response > 50%
Ruszniewski et al. ¹⁶	1993	23	18: CT 5: ICC	Adriamycin	73	57
Stokes et al. ²¹	1993	20	13: CT 7: ICC	Adriamycin	100	90
Therasse et al. ¹⁷	1993	23	Carcinoid	Adriamycin	100	91
Perry et al. ²²	1994	39	Carcinoid	Adriamycin	90	79
Clouse et al. ²⁰	1994	14	Carcinoid	Adriamycin	90	69
Diacio et al. ¹⁹	1995	10	Carcinoid	Cisplatin, mitomycin, adriamycin	100	—
Diamandidou et al. ²³	1998	20	17: CT 3: ICC	Cisplatin	67	73
Drougas et al. ²⁴	1998	15	Carcinoid	Cisplatin, mitomycin, adriamycin	67	100
Desai et al. ²⁵	2000	34	Carcinoid	Adriamycin, mitomycin	78	60
Dominguez et al. ¹³	2000	15	8: CT 7: ICC	Streptozocin	60 75	50
Ruszniewski and Malka ²⁶	2000	15	8: CT 7: ICC	Streptozocin	67	50
Roche et al. ¹⁸	2003	14	10: CT 4: Other	Adriamycin	70	75
Roche et al. ²⁷	2004	64	CT/ICC	Adriamycin	59	—
Touzios et al. ²⁸	2005	18	8: CT	Cisplatin, mitomycin, adriamycin	88	—
Marrache et al. ²⁹	2007	67	48: CT 19: ICC	Streptozocin, adriamycin	91	65
Ho et al. ³⁰	2007	46	31: CT 15: ICC	Cisplatin, mitomycin, adriamycin	78 75	—

Abbreviations: CT, carcinoid tumors; ICC, islet cell tumors.

Kvols et al.

Table 3 Objective Response of Metastatic Neuroendocrine Tumors Based on Therapy Received

Study	Year	Tumor Histology	Therapy	CR + PR %
Hajarizadeh et al. ³¹	1992	Carcinoid	TACE	50 (4 of 8)
Ruszniewski et al. ¹⁶	1993	Carcinoid	TACE	33.3 (6 of 18)
Therasse et al. ¹⁷	1993	Carcinoid	TACE	35 (6 of 17)
Clouse et al. ²⁰	1994	Carcinoid/ICC	TACE	95 (19 of 20)
Diacio et al. ¹⁹	1995	Carcinoid	TACE	60 (6 of 10)
Drougas et al. ²⁴	1998	Carcinoid	TACE	6.7 (1 of 15)
Kim et al. ³²	1999	Carcinoid	TACE	25 (4 of 16)
Dominguez et al. ¹³	2000	Carcinoid	TACE	50 (4 of 8)
Roche et al. ¹⁸	2003	Carcinoid	TACE	43 (6 of 14)
Gupta et al. ³³	2003	Carcinoid	TACE	44.4 (12 of 27)
Desai et al. ²⁵	2001	Carcinoid/ICC	TACE	45 (18 of 34)
Kress et al. ³⁴	2003	Carcinoid/ICC	TACE	7 (2 of 26)
Fiorentini et al. ³⁵	2004	Carcinoid/ICC	TACE	70 (7 of 10)
Marrache et al. ²⁹	2007	Carcinoid/ICC	TACE	37 (14 of 38)
Artinyan et al. ³⁶	2008	Carcinoid/ICC	TACE	22 (6 of 27)
Carrasco et al. ³⁷	1983	ICC	TACE	100 (3 of 3)
Mavligit et al. ³⁸	1993	ICC	TACE	80 (4 of 5)
Ruszniewski et al. ¹⁶	1993	ICC	TACE	0 (0 of 5)
Kim et al. ³²	1999	ICC	TACE	50 (7 of 14)
Dominguez et al. ¹³	2000	ICC	TACE	57 (4 of 7)
Gupta et al. ³³	2003	ICC	TACE	50 (11 of 22)
Carrasco et al. ³⁷	1983	Carcinoid	TAE (+ IFN)	83 (5 of 6)
Hanssen et al. ³⁹	1989	Carcinoid	TAE	71 (5 of 7)
Moertel et al. ¹	1994	Carcinoid	TAE	69.6 (16 of 23)
Wangberg et al. ⁴⁰	1996	Carcinoid	TAE	42.5 (17 of 40)
Eriksson et al. ⁴¹	1998	Carcinoid	TAE	38 (11 of 29)
Loewe et al. ⁴²	2003	Carcinoid	TAE	73 (16 of 22)
Gupta et al. ³³	2003	Carcinoid	TAE	81 (34 of 42)
Strosberg et al. ¹¹	2006	Carcinoid/ICC	TAE	48 (11 of 23)
Carrasco et al. ³⁷	1983	ICC	TAE	50 (3 of 6)
Moertel et al. ¹	1994	ICC	TAE	82 (14 of 17)
Eriksson et al. ⁴¹	1998	ICC	TAE	17 (2 of 12)
Gupta et al. ³³	2003	ICC	TAE	28 (9 of 32)
Ajani et al. ³	1988	ICC	TAE	60 (12 of 20)
Ho et al. ³⁰	2007	Carcinoid/ICC	TACE/TAE	46 (15 of 33)
Ruutiainen et al. ⁴³	2007	Carcinoid/ICC	TACE/TAE	49
Christante et al. ⁴⁴	2008	Carcinoid/ICC	TACE + chemo-infusion	80 (62 of 77)
McStay et al. ⁴⁵	2005	Carcinoid/ICC	Y-90 radioembolization	16 (3 of 19)
King et al. ⁴⁶	2008	Carcinoid/ICC	Y-90 radioembolization	50 (17 of 34)
Kennedy et al. ⁴⁷	2008	Carcinoid/ICC	Y-90 radioembolization	63.2 (93 of 148)
Murthy et al. ⁴⁸	2008	Carcinoid/ICC	Y-90 radioembolization	12 (1 of 8)

Abbreviations: ICC, islet cell tumors; CR, complete response; IFN, interferon alpha; PR, partial response; TACE, transarterial chemoembolization; TAE, transarterial (bland) embolization; Y-90, yttrium 90.

resin and is converted to yttrium 90 through neutron bombardment. Patients with myelosuppression and renal failure are generally excluded.

Preprocedural studies, including visceral angiogram for mapping the vascular supply to the liver, is performed approximately a week before radioembolization. Any vessels supplying the gastrointestinal tract that must be avoided are embolized before treatment. Technetium 99m isotope-labeled macro-albumin similar in size to the radioembolization particle is then infused through the catheter, and single-photon emission computed tomography (SPECT) gamma imaging is obtained to evaluate for possible shunting of microspheres to the lungs or gastrointestinal tract. The approach to radioembolization is similar to hepatic artery embolization. However, the goal of radioembolization is to cause tumor necrosis through radiation exposure. Cell death through radiation requires normal oxygen tension. Therefore, stasis of flow is avoided during radioembolization. Radioembolic agents are typically infused to both lobes rather than staged using a unilobar approach.

In a retrospective multi-institutional study, radioembolization showed complete imaging response in 2.7% of cases, partial response in 60.5%, stable disease in 22.7%, disease progression in 4.9%, and median survival of 70 months.⁴⁷ A study comparing the use of glass versus resin microspheres for metastatic neuroendocrine tumors showed a 92% and 94% response rate at 6 months, with a median survival of 22 and 28 months, respectively. Grade III/IV toxicity was experienced by 14% of patients.⁴⁹ The side effect profile includes renal failure, postembolization syndrome, and bone marrow suppression. The postembolization syndrome occurs in only 18% of cases due to arterial flow stasis.

Radiofrequency Ablation, Cryoablation, and Percutaneous Alcohol Injection

Patients with limited numbers of unresectable liver metastases may benefit from interventional ablative techniques. Tumor ablations are often performed intraoperatively, in conjunction with surgical resection. Alternatively, they may be performed percutaneously, depending on the number and location of the hepatic metastases.

Radiofrequency Ablation

Radiofrequency ablation (RFA) involves converting

radiofrequency waves to heat using a high alternating current of 460 kHz, which passes from an uninsulated tip into surrounding tissues and causes ionic vibration after the change in the direction of the current. Friction heating caused by the ionic vibration and tumor death occurs at around 60°C. The size of the ablation zone is dependent on the size of the probe. Currently the largest ablation zone is approximately 7 cm.

Technique

RFA can be performed under local anesthesia with sedation or under general anesthesia. Using ultrasound or CT image guidance, an RFA needle probe is inserted into the liver metastasis. The position of the probe is confirmed on multiplanar imaging to verify true centricity of the probe. The tines of the probe (e.g., RITA Angiodynamics, Queensbury, New York; Cooltip RFA device, Valleylab, Colorado; RF 3000, Boston Scientific, Natick, Massachusetts) are then advanced to generate a thermal ablation zone, including the tumor and a margin. Anatomic proximity to blood vessels can act as a heat sink, thus causing loss of effect, and temperatures are continuously monitored on each of the probe tines. Once adequate heating is achieved for the specified duration based on size of the ablation zone, the tines are withdrawn and the probe removed. Similar procedures are repeated for other lesions.

Patients are usually monitored postoperatively for pain and fevers. Other complications include bile leakage and pleural effusion.⁵⁰ Radiologic follow-up is established and the images are reviewed by an experienced radiologist.

Response

Complete or significant symptom response has been shown in 69% to 80% of patients treated with RFA, and local control was achieved in 74% of the symptomatic patients.¹² Complications associated with RFA are usually restricted to those at the site of needle entry, such as pneumothorax and neuritis, in addition to liver abscesses.

Percutaneous Ethanol Injection

Percutaneous alcohol ablation has been described in the treatment of hepatocellular carcinoma and metastatic colorectal adenocarcinomas, in which necrosis is achieved in 50% of cases.^{51,52} Alcohol acts by causing coagulative necrosis, which then leads to thrombosis of small vessels accompanied by formation of fibrotic tissue. The main concern regarding ethanol

use is its inhomogenous distribution. Overall, percutaneous ethanol injection has largely been replaced by RFA, which typically achieves necrosis in fewer sessions and is associated with lower rates of recurrence.^{52,53} Therefore ethanol ablation is generally reserved for metastases abutting large vessels susceptible to the heat-sink effect, and adjacent to central bile ducts in which strictures can occur with RFA.⁵⁴

Cryoablation

Cryoablation involves freezing and thawing of tumors, resulting in tumor ablation.^{55–59} Cryotherapy can be used percutaneously or intraoperatively using intraoperative ultrasound and probes, and has become an important adjunct to surgical cytoreduction. Drawbacks include the large size of the probe, which causes increased risk for hemorrhage and higher rates of complications for larger metastases. More recently, smaller-gauge cryoprobes for percutaneous ablation, which allow placement of multiple probes, have been introduced simultaneously (PerCryo, Endocare Inc, Irvine, California). Image guidance is improved with use of CT, which clearly delineates the iceball for accurate visualization of the zone of treatment. Limited data remain for cryoablation treatment of neuroendocrine liver metastases, but it has potential and requires further investigation by interventional radiologists.

Laser Interstitial Thermotherapy

Using a Nd-YAG laser to create coagulative necrosis has been proposed for managing hepatic metastasis from neuroendocrine tumors. The laser fiber is introduced through a laser application kit, consisting of a cannulation needle, guide wire, sheath system with mandrin (10F, 20 cm in length), and special protective catheter (9F, 43 cm in length) that is closed at the end. This protective catheter, which is heat-resistant, prevents direct contact of the laser fiber with the tissue and enables safe and easy removal of the fiber post-therapy. The laser system is cooled with saline and therefore prevents carbonization of the laser fiber. The advantage of the laser application system is that it can be performed under MR guidance; this is of great value because the efficacy of the therapy can be evaluated simultaneously using MRI.⁶⁰

Conclusions

The role of interventional radiologists in managing liver metastasis from neuroendocrine tumors is inte-

gral to multidisciplinary care. Available techniques for patients with disseminated hepatic metastases include hepatic arterial embolization, chemoembolization, and radioembolization. RFA, cryotherapy, and, to a lesser extent, ethanol therapy serve as adjuncts to surgical cytoreduction when necessary.

References

1. Moertel CG, Johnson CM, McKusick MA, et al. The management of patients with advanced carcinoid tumors and islet cell carcinomas. *Ann Intern Med* 1994;120:302–309.
2. Carrasco CH, Charnsangavej C, Ajani J, et al. The carcinoid syndrome: palliation by hepatic artery embolization. *AJR Am J Roentgenol* 1986;147:149–154.
3. Ajani JA, Carrasco CH, Charnsangavej C, et al. Islet cell tumors metastatic to the liver: effective palliation by sequential hepatic artery embolization. *Ann Intern Med* 1988;108:340–344.
4. Clark OH, Ajani JA, Benson AB, et al. NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. Version 1, 2008. Available at: www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf. Accessed January 3, 2009.
5. Proye C. Natural history of liver metastasis of gastroenteropancreatic neuroendocrine tumors: place for chemoembolization. *World J Surg* 2001;25:685–688.
6. Blonski WC, Reddy KR, Shaked A, et al. Liver transplantation for metastatic neuroendocrine tumor: a case report and review of the literature. *World J Gastroenterol* 2005;11:7676–7683.
7. Sutcliffe R, Maguire D, Ramage J, et al. Management of neuroendocrine liver metastases. *Am J Surg* 2004;187:39–46.
8. Pichlmayr R, Weimann A, Oldhafer KJ, et al. Appraisal of transplantation for malignant tumours of the liver with special reference to early stage hepatocellular carcinoma. *Eur J Surg Oncol* 1998;24:60–67.
9. Le Treut YP, Delpero JR, Dousset B, et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. *Ann Surg* 1997;225:355–364.
10. Venook AP. Embolization and chemoembolization therapy for neuroendocrine tumors. *Curr Opin Oncol* 1999;11:38–41.
11. Strosberg JR, Choi J, Cantor AB, Kvols LK. Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors. *Cancer Control* 2006;13:72–78.
12. Ruzniewski P. Interventional radiology: less invasive or less effective? In: Irvin M, Modlin KO, eds. *A Century of Advances in Neuroendocrine Tumor Biology and Treatment*. Hanover, Germany: Felsenstein CCCP; 2007.
13. Dominguez S, Denys A, Madeira I, et al. Hepatic arterial chemoembolization with streptozotocin in patients with metastatic digestive endocrine tumours. *Eur J Gastroenterol Hepatol* 2000;12:151–157.
14. Casadei R, Tomassetti P, Rossi C, et al. Treatment of metastatic glucagonoma to the liver: case report and literature review. *Ital J Gastroenterol Hepatol* 1999;31:308–312.
15. Lee SM, Forbes A, Williams R. Metastatic islet cell tumour with clinical manifestations of insulin and glucagon excess: successful treatment by hepatic artery embolization and chemotherapy. *Eur J Surg Oncol* 1988;14:265–268.

Interventional Radiology for Neuroendocrine Liver Metastases

16. Ruszniewski P, Rougier P, Roche A, et al. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors. A prospective phase II study in 24 patients. *Cancer* 1993;71:2624–2630.
17. Therasse E, Breittmayer F, Roche A, et al. Transcatheter chemoembolization of progressive carcinoid liver metastasis. *Radiology* 1993;189:541–547.
18. Roche A, Girish BV, de Baere T, et al. Trans-catheter arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumors. *Eur Radiol* 2003;13:136–140.
19. Diaco DS, Hajarizadeh H, Mueller CR, et al. Treatment of metastatic carcinoid tumors using multimodality therapy of octreotide acetate, intra-arterial chemotherapy, and hepatic arterial chemoembolization. *Am J Surg* 1995;169:523–528.
20. Clouse ME, Perry L, Stuart K, Stokes KR. Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. *Digestion* 1994;55(Suppl 3):92–97.
21. Stokes KR, Stuart K, Clouse ME. Hepatic arterial chemoembolization for metastatic endocrine tumors. *J Vasc Interv Radiol* 1993;4:341–345.
22. Perry LJ, Stuart K, Stokes KR, Clouse ME. Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. *Surgery* 1994;116:1111–1116; discussion 1116–1117.
23. Diamandidou E, Ajani JA, Yang DJ, et al. Two-phase study of hepatic artery vascular occlusion with microencapsulated cisplatin in patients with liver metastases from neuroendocrine tumors. *AJR Am J Roentgenol* 1998;170:339–344.
24. Drougas JG, Anthony LB, Blair TK, et al. Hepatic artery chemoembolization for management of patients with advanced metastatic carcinoid tumors. *Am J Surg* 1998;175:408–412.
25. Desai DC, O'Dorisio TM, Schirmer WJ, et al. Serum pancreastatin levels predict response to hepatic artery chemoembolization and somatostatin analogue therapy in metastatic neuroendocrine tumors. *Regul Pept* 2001;96:113–117.
26. Ruszniewski P, Malka D. Hepatic arterial chemoembolization in the management of advanced digestive endocrine tumors. *Digestion* 2000;62(Suppl 1):79–83.
27. Roche A, Girish BV, de Baere T, et al. Prognostic factors for chemoembolization in liver metastasis from endocrine tumors. *Hepatogastroenterology* 2004;51:1751–1756.
28. Touzios JG, Kiely JM, Pitt SC, et al. Neuroendocrine hepatic metastases: does aggressive management improve survival? *Ann Surg* 2005;241:776–783; discussion 783–775.
29. Marrache F, Vullierme MP, Roy C, et al. Arterial phase enhancement and body mass index are predictors of response to chemoembolisation for liver metastases of endocrine tumours. *Br J Cancer* 2007;96:49–55.
30. Ho AS, Picus J, Darcy MD, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. *AJR Am J Roentgenol* 2007;188:1201–1207.
31. Hajarizadeh H, Ivancev K, Mueller CR, et al. Effective palliative treatment of metastatic carcinoid tumors with intra-arterial chemotherapy/chemoembolization combined with octreotide acetate. *Am J Surg* 1992;163:479–483.
32. Kim YH, Ajani JA, Carrasco CH, et al. Selective hepatic arterial chemoembolization for liver metastases in patients with carcinoid tumor or islet cell carcinoma. *Cancer Invest* 1999;17:474–478.
33. Gupta S, Yao JC, Ahrar K, et al. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. *Cancer J* 2003;9:261–267.
34. Kress O, Wagner HJ, Wied M, et al. Transarterial chemoembolization of advanced liver metastases of neuroendocrine tumors—a retrospective single-center analysis. *Digestion* 2003;68:94–101.
35. Fiorentini G, Rossi S, Bonechi F, et al. Intra-arterial hepatic chemoembolization in liver metastases from neuroendocrine tumors: a phase II study. *J Chemother* 2004;16:293–297.
36. Artinyan A, Nelson R, Soriano P, et al. Treatment response to transcatheter arterial embolization and chemoembolization in primary and metastatic tumors of the liver. *HPB (Oxford)* 2008;10:396–404.
37. Carrasco CH, Chuang VP, Wallace S. Apudomas metastatic to the liver: treatment by hepatic artery embolization. *Radiology* 1983;149:79–83.
38. Mavligit GM, Pollock RE, Evans HL, Wallace S. Durable hepatic tumor regression after arterial chemoembolization-infusion in patients with islet cell carcinoma of the pancreas metastatic to the liver. *Cancer* 1993;72:375–380.
39. Hanssen LE, Schrumpf E, Kolbenstvedt AN, et al. Recombinant alpha-2 interferon with or without hepatic artery embolization in the treatment of midgut carcinoid tumours. A preliminary report. *Acta Oncol* 1989;28:439–443.
40. Wangberg B, Westberg G, Tylen U, et al. Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction. *World J Surg* 1996;20:892–899; discussion 899.
41. Eriksson BK, Larsson EG, Skogseid BM, et al. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer* 1998;83:2293–2301.
42. Loewe C, Schindl M, Cejna M, et al. Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and lipiodol: assessment of mid- and long-term results. *AJR Am J Roentgenol* 2003;180:1379–1384.
43. Ruutuinen AT, Soulen MC, Tuite CM, et al. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. *J Vasc Interv Radiol* 2007;18:847–855.
44. Christante D, Pommier S, Givi B, Pommier R. Hepatic artery chemoinfusion with chemoembolization for neuroendocrine cancer with progressive hepatic metastases despite octreotide therapy. *Surgery* 2008;144:885–893; discussion 893–884.
45. McStay MK, Maudgil D, Williams M, et al. Large-volume liver metastases from neuroendocrine tumors: hepatic intraarterial 90Y-DOTA-lanreotide as effective palliative therapy. *Radiology* 2005;237:718–726.
46. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer* 2008;113:921–929.
47. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol* 2008;31:271–279.
48. Murthy R, Kamat P, Nunez R, et al. Yttrium-90 microsphere radioembolotherapy of hepatic metastatic neuroendocrine carcinomas after hepatic arterial embolization. *J Vasc Interv Radiol* 2008;19:145–151.
49. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. *Ann Surg* 2008;247:1029–1035.

Kvols et al.

-
50. Hellman P, Ladjevardi S, Skogseid B, et al. Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine tumors. *World J Surg* 2002;26:1052–1056.
  51. Giovannini M. Percutaneous alcohol ablation for liver metastasis. *Semin Oncol* 2002;29:192–195.
  52. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999;210:655–661.
  53. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003;228:235–240.
  54. Atwell TD, Charboneau JW, Que FG, et al. Treatment of neuroendocrine cancer metastatic to the liver: the role of ablative techniques. *Cardiovasc Intervent Radiol* 2005;28:409–421.
  55. Shafir M, Shapiro R, Sung M, et al. Cryoablation of unresectable malignant liver tumors. *Am J Surg* 1996;171:27–31.
  56. Cozzi PJ, Englund R, Morris DL. Cryotherapy treatment of patients with hepatic metastases from neuroendocrine tumors. *Cancer* 1995;76:501–509.
  57. Sheen AJ, Poston GJ, Sherlock DJ. Cryotherapeutic ablation of liver tumours. *Br J Surg* 2002;89:1396–1401.
  58. Duperier T, Ali A, Pereira S, et al. Laparoscopic cryoablation of a metastatic carcinoid tumor. *J Laparoendosc Adv Surg Tech A* 2001;11:105–109.
  59. Shapiro RS, Shafir M, Sung M, et al. Cryotherapy of metastatic carcinoid tumors. *Abdom Imaging* 1998;23:314–317.
  60. Vogl TJ, Naguib NN, Zangos S, et al. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol* 2009; in press.