Annie Toja. *French Riviera, Olive Trees.* Acrylic.

Hepatic artery embolization often results in regressions in patients with unresectable liver metastases from carcinoid or pancreatic endocrine tumors.

Selective Hepatic Artery Embolization for Treatment of Patients With Metastatic Carcinoid and Pancreatic Endocrine Tumors

Jonathan R. Strosberg, MD, Junsung Choi, MD, Alan B. Cantor, PhD, and Larry K. Kvols, MD

Background: *Prognosis in patients with carcinoid and pancreatic endocrine tumors with diffuse, unresectable liver metastases is poor. Palliation is often difficult despite the use of somatostatin analogs, interferon alpha, or systemic chemotherapy. Several reviews have suggested that hepatic artery embolization, with or without intraarterial chemotherapy, can be used for control of symptoms and for cytoreduction in patients with liver-dominant metastases.*

Methods: *Between 2000 and 2002, 161 embolizations using polyvinyl alcohol or microspheres were performed on 84 patients with carcinoid or pancreatic endocrine tumors metastatic to the liver. A retrospective review was performed to evaluate symptomatic response, biochemical response, adverse effects, and duration of survival. Baseline and follow-up computed tomography scans were also assessed to determine radiographic response rates. Further analysis of survival was performed to assess the possible impact of various post-embolization therapies.*

Results: *Eighty-four patients underwent bland hepatic artery embolizations during the study period. Among 55 symptomatic patients, 44 patients had fewer symptoms, and among 35 patients whose tumor markers were followed, 28 had a major biochemical response. Objective radiographic responses were observed in 11 of 23 patients. No deaths occurred during therapy, and major toxicities were rare. Median overall survival was 36 months from time of initial embolization.*

Conclusions: *Hepatic artery embolization frequently results in clinical and radiographic responses in patients with unresectable liver metastases from carcinoid or pancreatic endocrine tumors. Morbidity is low when appropriate supportive care is provided.*

Introduction

Carcinoid tumors and pancreatic endocrine tumors often metastasize to the liver. At this stage of disease, they may produce symptoms due to hormonal secretion and/or tumor burden. Bulky liver metastases are frequently associated with poor survival and reduced quality of life.[1-4]

Although surgical resection is generally the procedure of choice for patients with localized hepatic metastases, it is rarely an option for patients with disseminated or multifocal disease.[1,5-13] Other liver-directed therapies include cryotherapy and radiofrequency ablation.[10,14-18] These modalities are effective for treating small, localized hepatic metastases. Liver transplantation is rarely an option for patients with metastatic neuroendocrine tumors.[19,20]

Systemic chemotherapy and interferon have been evaluated extensively. In well-differentiated carcinoid tumors, response rates are disappointing when strict radiographic criteria are employed.[21-38] The efficacy of cytotoxic treatment appears to be somewhat higher in pancreatic endocrine tumors with approximately 40% of patients responding to combination chemotherapy.[39-42]

Somatostatin analogs are highly effective at controlling carcinoid syndrome and other hormonally associated symptoms.[43-47] Moreover, in vitro and in vivo studies of somatostatin analogs demonstrate an antiproliferative effect on neuroendocrine tumor cells.[48-50] In clinical practice, however, objective tumor responses are rarely seen with these agents.[1,9,48]

The theoretical rationale for hepatic artery embolization is based on the observation that these hypervascular tumors derive the majority of their blood supply from the hepatic artery. Conversely, normal liver tissue derives its blood supply primarily from the portal vein.[51-53] Both bland hepatic embolizations (using microparticles) and chemoembolizations (with addition of intra-arterial chemotherapy) are increasingly used in the management of bulky and disseminated hepatic metasteses.[3,51-58] There are no studies comparing the two techniques.

Early attempts at hepatic artery occlusion, either surgically or via embolization, demonstrated response rates exceeding 50%. However, these procedures were associated with relatively high morbidity.[52,53] Recently, the technique of selective hepatic embolization has developed, whereby the left or right hepatic arterial branches arising from the proper hepatic artery are embolized separately. This selective procedure is thought to reduce morbidity compared with single-stage embolization or ligation of the common hepatic artery.

At our institute, we began routinely performing bland, selective hepatic artery embolizations in January 2000. Over the ensuing 3 years, 84 patients with metastatic carcinoid and pancreatic neuroendocrine tumors underwent this procedure. In this study, we retrospectively analyze clinical, biochemical, and radiographic response rates as well as overall survival. Further survival analysis of postembolization treatment with chemotherapy and with radiolabeled octreotide analogs is performed. Finally, we examine the effects of somatostatin analog therapy on survival in this cohort of patients.

Patients and Methods

Patients

We retrospectively evaluated the medical records of all patients with carcinoid and pancreatic endocrine tumors who underwent bland liver embolizations at our institute between January 2000 and December 2002. Approvals for retrospective chart review were obtained from the Institutional Review Board.

Embolization Procedure

Eligibility requirements included intact liver and renal function (bilirubin <2 mg/dL, serum creatinine level <2 mg/dL). Absolute contraindications were portal vein occlusion and ascites. All patients were admitted to the hospital prior to the procedure and started on intravenous hydration. Subcutaneous octreotide was administered immediately before the procedure. Prior to embolization, a celiac angiogram was performed to identify the hepatic vasculature and ensure patency of the portal vein. Superior mesenteric artery angiogram was performed if needed to evaluate for accessory or replaced hepatic arteries supplying the liver. Subselective catheterization of the right or left hepatic artery was performed using a 3F microcatheter (Tracker 18, Boston Scientific, Boston, Mass) coaxially through a 5F angled catheter (Soft Vu-Hook, Angiodynamics, Queensbury, NY) placed in the origin of the celiac artery or the superior mesenteric artery.

Hepatic arterial embolization was then performed under fluoroscopy, using either 250–355 micron diameter polyvinyl alcohol (Contour particles, Boston Scientific-Target Vascular, Boston, Mass) or 500–700 micron diameter microspheres (Embosphere microspheres, Biosphere Medical, Inc, Rockland, Mass) as the particulate material. Embolization was performed until the selected vessel demonstrates complete or near complete stasis of flow. Usually the liver lobe with the bulkiest disease was embolized first.

After embolization, patients were monitored in the hospital and discharged only after their liver enzymes had peaked. All patients were prophylactically administered levofloxacin and metronidazole for one week in order to prevent abscess formation. Intravenous narcotics were typically administered for pain control. Individual embolizations were spaced approximately 4

weeks apart and the majority of patients completed their embolizations in 2 or 3 stages.

Results

Patient Characteristics

During our study period, 84 patients (39 men and 45 women; age range 30–83 years; median age 58 years) with liver metastases from carcinoid tumors or pancreatic endocrine tumors underwent bland hepatic artery embolizations. Fifty-nine patients had carcinoid tumors, 20 had pancreatic endocrine tumors, and 5 had neuroendocrine tumors with poorly differentiated histology. The median duration of disease from time of initial discovery of metastases was 2 years. Before embolization at our institution, 25 patients had been treated with chemotherapy, 4 had received interferon, and 7 had undergone prior embolization or chemoembolization. Seventy-one patients received long-term ongoing treatment with a somatostatin analog starting before, during, or shortly after their embolization (Table 1).

Although all patients had predominance of metastatic disease in the liver, 22 patients (26%) also had extrahepatic metastases at the time of embolization. Sites of metastases included lymph nodes, bone, lung, spleen, and brain. Primary tumors had been surgically removed in 42 patients (50%) prior to embolization. The majority of patients with carcinoid tumors (60%) underwent resection of their primary tumor site (usually small bowel), whereas only one quarter of patients with pancreatic endocrine tumors underwent resection of the primary tumor site. Patient demographics are summarized in Table 1.

Table 1. — Patient Demographics and Tumor Characteristics

Demographics	No. of Patients (N = 84)
Median age (range)	58 yrs (30–83)
Gender ratio (M/F))	39/45
Median years from diagnosis of liver metastases (range)	2 (0–22)
Tumor type:	
Carcinoid	59
Pancreatic endocrine	20
Poorly differentiated histology	5
Prior treatment:	
Systemic chemotherapy or immunotherapy	29
Hepatic embolization or chemoembolization	7
Octreotide	62
Extrahepatic metastases (n = 22):	
Lymph node	11
Bone	7
Lung	2
Spleen	1
Brain	1
Primary tumor:	
Resected	42
Unresected or occult	42

Table 2. — Pretreatment Clinical Symptoms

Symptoms	No. of Patients (N = 84)
Diarrhea and/or flushing	41 (49%)
Abdominal pain	14 (17%)
Fatigue	4 (5%)
Hypoglycemia	2 (2%)
Hyperglycemia	2 (2%)
Asymptomatic	21 (25%)

Indications for treatment included flushing, diarrhea, or abdominal pain in the majority of patients. Pretreatment symptoms are listed in Table 2. Twenty-one patients (25%) had no appreciable symptoms at the time of embolization and underwent the procedure solely for tumor cytoreduction.

Treatment

The 84 patients underwent a total of 161 embolization treatments. Twenty-one patients were treated with a single embolization, 51 had two-stage embolizations, 10 had three-stage embolizations, and 2 required four embolizations. Following embolization, 13 patients were given cytotoxic chemotherapy and 10 were enrolled in clinical trials of yttrium- or lutetium-labeled somatostatin analogs.

Radiographic and Biochemical Response

Twenty-three patients were evaluated by baseline and follow-up imaging. Of these patients, 11 (48%) had partial response and 12 (52%) had stable disease using response evaluation criteria in solid tumors (RECIST).

Tumor markers (5-HIAA, chromogranin, pancreatic polypeptide or insulin) were available at baseline and follow-up in 35 patients. Of these, 28 patients (80%) had a major response (>50% reduction), 4 patients (11%) had a minor response (25%–50%), and 3 patients (9%) had no response.

Clinical Response

Twenty-one patients had no significant symptomatology prior to the procedure. In an additional 8 patients, clinical benefit could not be ascertained due to poor follow-up. Among the remaining 55 patients, 44 (80%) experienced symptomatic improvement, whereas only 11 (20%) derived no symptomatic benefit from embolization. Response categories included improvement in flushing and diarrhea (21 patients), abdominal pain (11 patients), and glucose control (3 patients), as well as nonspecific symptomatic improvement (9 patients).

Response to Repeat Embolization

Seven patients had prior embolizations, and 14 additional patients went on to receive further embolizations after their initial series. Among those with clearly
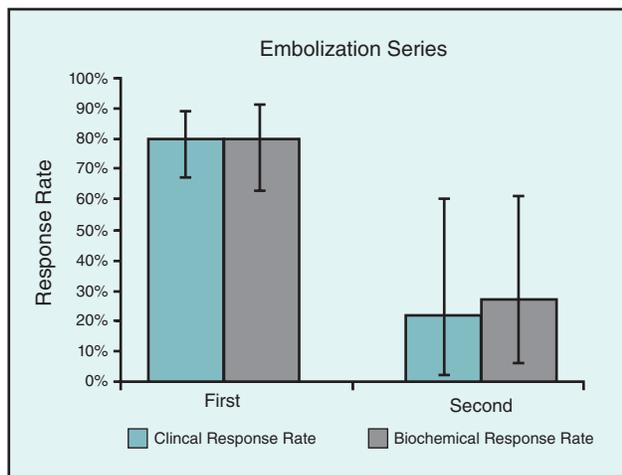
Fig 1. — Clinical and biochemical response rates after first embolization series compared with clinical and biochemical response rates after second embolization series.

documented follow-up, only 2 of 9 patients (0.22, 95% confidence interval [CI] 0.02–0.60) derived symptomatic benefit from a repeat embolization series, and only 3 of 11 patients (0.27, 95% CI 0.06–0.61) had a major biochemical response (Fig 1).

Adverse Effects

All patients experienced postembolization syndrome to some extent, including abdominal pain (often pleuritic right upper-quadrant pain), nausea, fevers, and transaminitis. Liver enzymes typically peaked within 2 to 3 days (median baseline aspartate aminotransferase [AST] 35 mg/dL; median peak AST 333 mg/dL) and receded back to preembolization levels at the time of follow-up several weeks after embolization. Patients were hospitalized until liver enzymes peaked, resulting in a median hospital stay of 4 days.

Severe hypertension (systolic blood pressure >180) was observed in 9 patients (11%), each of whom had hormonally active carcinoid tumors. These episodes of hypertension typically began during the embolization procedure.
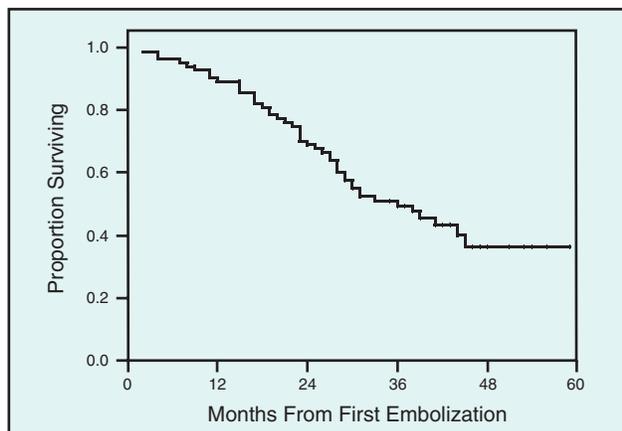
Unusual adverse effects were noted in 4 additional patients. One patient had a myocardial infarction, another had transient thrombocytopenia (nadir platelet count of 40×10^9/L), a liver hematoma occurred in 1 patient, and bilateral pleural effusions were observed in 1 patient. No deaths occurred at the time of embolization. Two patients died 2 months after embolization due to unknown reasons.

Overall Survival

Overall survival was calculated for all patients from the time of first embolization at our institution. At a median of 42 months follow-up, 46 patients had died and 38 patients were alive (Fig 2). Median overall survival was 36 months (95% CI 28–45 months).

Overall survival differed by histology (Fig 3). Survival was 44 months (95% CI 33–55 months) for patients with carcinoid tumors, 31 months (95% CI 21–42 months) for those with pancreatic endocrine tumors, and 15 months (95% CI 0–39 months) for patients with poorly differentiated histology. Survival differences were statistically significant.

Postembolization Therapy

Survival was further analyzed to ascertain the effects of postembolization chemotherapy and radiopharmaceutical therapy. The 5 patients with poorly differentiated histology were excluded from this analysis. Chemotherapy was prescribed for 13 patients after their embolizations with the intention of improving progression-free survival. Of these 13 patients, 10 had pancreatic endocrine tumors, whereas only 3 had carcinoid tumors. The majority of these patients received alternating cycles of doxorubicin with dacarbazine and streptozocin with 5-fluorouracil. The overall survival of patients who received postembolization chemotherapy was 38 months (95% CI 24–52 months), whereas the overall survival for those patients who did not receive chemotherapy after embolization was 44 months (95% CI 32–56 months) (Fig 4).

Fig 2. — Overall survival from time of first embolization at our institution. Median survival was 36 months (95% CI 28-45 months).
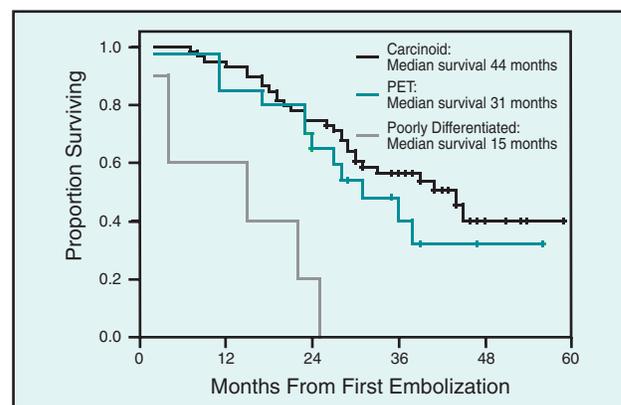

Fig 3. — Overall survival from time of first embolization, by diagnosis. Median survival was 44 months for carcinoid tumors, 31 months for pancreatic endocrine tumors, and 15 months for poorly differentiated tumors.

After embolization, 10 patients enrolled in clinical trials testing peptide receptor radionuclide therapy with either yttrium or lutetium coupled to a somatostatin analog. Median survival has not yet been reached for these patients (Fig 5).

Somatostatin Analog Therapy

Survival was analyzed to ascertain the effect of somatostatin analog therapy. Patients with poorly differentiated histology were excluded from this analysis. Among the remaining patients, 67 received long-term therapy with a somatostatin analog, typically starting prior to embolization. Median survival in this cohort was 41 months (95% CI 30–52 months). Twelve patients did not receive long-term somatostatin analog therapy. These patients typically had nonfunctioning neuroendocrine tumors. Among these patients, median survival was 24 months (95% CI 17–31 months) (Fig 6).

Discussion

Patients with advanced hepatic metastases from carcinoid or pancreatic endocrine tumors have few treatment options. Many have incapacitating hormonal symptoms despite somatostatin analog therapy or have abdominal pain related to tumor mass. In our study, we demonstrated a clinical response in 80% of symptomatic patients undergoing embolization. This clinical response rate closely corresponds to an 80% major biochemical response rate as measured by reduction in tumor markers by more than half. The radiographic partial response rate of 48% is similar to that demonstrated in other reviews of hepatic artery embolization. Moreover, this study used RECIST criteria for calculation of radiographic response, unlike several prior studies in which measures of response were not as strict.

The response rates achieved with hepatic artery embolizations compare favorably to responses achieved with chemotherapy or immunotherapy. Moreover, the toxicity profile is manageable with appropriate supportive care, as illustrated by this study. Analysis of patients undergoing a second embolization series indicated a significant decrease in benefit after repeat embolizations. Clinical and biochemical response rates after repeat embolizations were approximately 25%. The cause of this diminishing response is uncertain. It is possible that following embolization, tumors derive an increased supply of blood from the portal circulation or from diaphragmatic collaterals, therefore rendering hepatic artery embolization less effective.

Severe adverse effects were observed infrequently, and no deaths occurred in this study. Most patients experienced a postembolization syndrome with fever, nausea, abdominal pain, and elevated transaminase levels. Typically, this syndrome lasted approximately 3 to 4 days. There were 9 cases of severe hypertension, all in carcinoid patients, typically occurring during the actual embolization procedure. Past reports of embolization have not emphasized this complication, and the etiology is uncertain. Given this finding, it is important to closely monitor blood pressure and treat hypertension aggressively in carcinoid patients undergoing embolization.

Interestingly, no episodes of acute liver failure, liver abscesses, or hepatorenal syndrome occurred in this
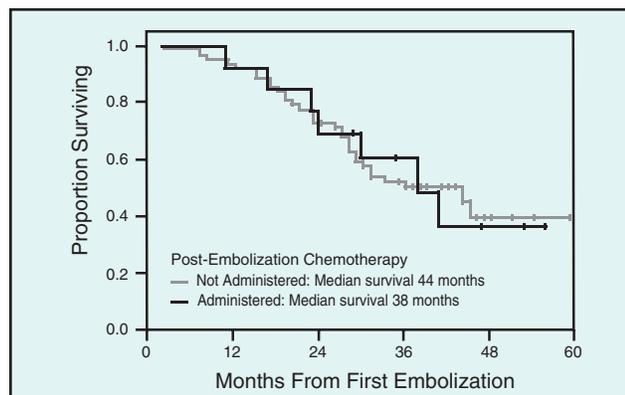

Fig 4. — Postembolization chemotherapy: overall survival from time of first embolization.
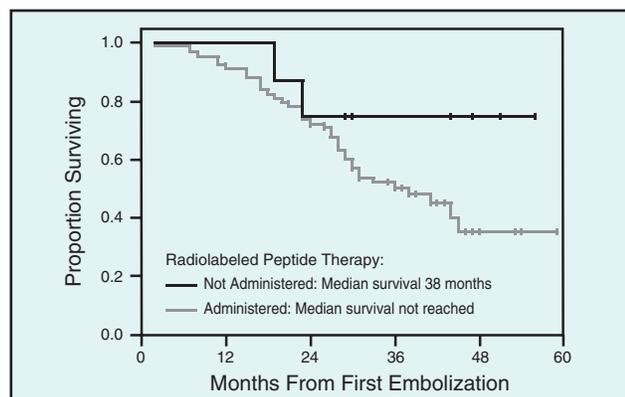

Fig 5. — Postembolization radiolabeled peptide therapy: overall survival from time of first embolization.
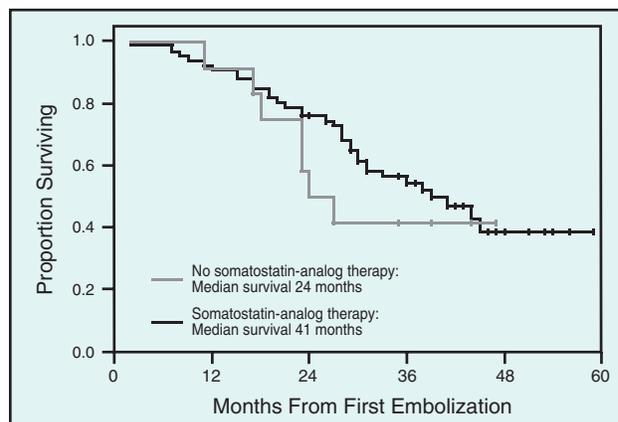

Fig 6. — Long-term somatostatin analog therapy: overall survival from time of first embolization.

cohort of patients. These complications have been described in past reports of embolization, particularly when the common hepatic artery was occluded.[52,53] Absence of these complications in this study may be due to the multistage technique, use of prophylactic antibiotics, and aggressive hydration.

In the present study, the median overall survival from the time of first embolization at our institution was 36 months. If patients with poorly differentiated histology are excluded, median survival was 40 months. This duration of survival is impressive by historical standards, especially considering the median interval of 2 years between diagnosis of metastatic disease and embolization.

The short survival among the cohort of patients with poorly differentiated histology (median 15 months) was similar to survival observed in prior studies. Thus, we would not recommend hepatic artery embolization for patients with this type of rapidly progressive neuroendocrine carcinoma. Systemic chemotherapy is more appropriate in treatment of this tumor subtype.[59]

An analysis of overall survival among patients receiving postembolization chemotherapy appeared to show a slight reduction in survival compared with patients who did not receive chemotherapy. This unexpected result may be due to a selection bias: of the 13 patients receiving chemotherapy after embolization, only 3 had carcinoid tumors, while 10 had pancreatic endocrine tumors, which typically confer a worse prognosis. Thus, it is difficult to draw conclusions on use of chemotherapy after embolization. At our institute, we commonly recommend this option to patients with pancreatic endocrine tumors but rarely to patients with carcinoid tumors.

Median survival has not yet been reached among patients receiving postembolization therapy with yttrium or lutetium conjugated to octreotide. It is hoped that this encouraging response will be validated by results of prospective studies using these experimental treatments.

The median survival of patients receiving long-term somatostatin analog therapy was 41 months compared with a median survival of 24 months among patients who did not receive this treatment. Selection bias may explain some of this difference (the pleurality of those who did not receive octreotide had nonfunctioning pancreatic endocrine tumors). However, in light of prior studies demonstrating the antiproliferative effect of somatostatin analogs, it remains a reasonable strategy to offer this treatment to most patients with carcinoid or pancreatic endocrine tumors. In our practice, we routinely administer somatostatin analog therapy to patients with tumor uptake on OctreoScans, indicating somatostatin receptor positivity.[60]

Future trials are needed to compare bland hepatic artery embolization with chemoembolization, to further address the role of postembolization chemotherapy, and to assess standard therapy vs new treatment

modalities such as radiopharmaceutical agents. Angiogenesis inhibiting agents may become important in treating this class of vascular tumors, possibly as postembolization therapy. Progress in the field will depend on prospective trials to address these issues.

References

1. Moertel CG. Karnofsky memorial lecture: an odyssey in the land of small tumors. *J Clin Oncol.* 1987;5:1502-1522.
2. Norheim I, Oberg K, Theodorsson-Norheim E, et al. Malignant carcinoid tumors: an analysis of 103 patients with regard to tumor localization, hormone production, and survival. *Ann Surg.* 1987;206:115-125.
3. 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.
4. Yao KA, Talamonti MS, Nemcek A, et al. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. *Surgery.* 2001;130:677-685.
5. Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg.* 1995;169:36-43.
6. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. *Surgery.* 1990;108:1091-1096.
7. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg.* 2003;197:29-37.
8. Dousset B, Saint-Marc O, Pitre J, et al. Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. *World J Surg.* 1996;20:908-915.
9. Kulke MH, Mayer RJ. Carcinoid tumors. *N Engl J Med.* 1999;340: 858-868.
10. O'Toole D, Maire F, Ruszniewski P. Ablative therapies for liver metastases of digestive endocrine tumours. *Endocr Relat Cancer.* 2003;10:463-468.
11. Norton JA, Warren RS, Kelly MG, et al. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery.* 2003;134:1057-1065.
12. Gulec SA, Mountcastle TS, Frey D, et al. Cytoreductive surgery in patients with advanced-stage carcinoid tumors. *Am Surg.* 2002;68:667-672.
13. Chung MH, Pisegna J, Spirt M, et al. Hepatic cytoreduction followed by a novel long-acting somatostatin analog: a paradigm for intractable neuroendocrine tumors metastatic to the liver. *Surgery.* 2001;130:954-962.
14. 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. Epub 2002 May 21.
15. Gillams A, Cassoni A, Conway G, et al. Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. *Abdom Imaging.* 2005;30:435-441.
16. Ruszniewski P, O'Toole D. Ablative therapies for liver metastases of gastroenteropancreatic endocrine tumors. *Neuroendocrinology.* 2004;80 (suppl 1):74-78.
17. Henn AR, Levine EA, McNulty W, et al. Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes. *AJR Am J Roentgenol.* 2003;181:1005-1010.
18. Mazziotti A, Grazi GL, Gardini A, et al. An appraisal of percutaneous treatment of liver metastases. *Liver Transpl Surg.* 1998;4:271-275.
19. Sutcliffe R, Maguire D, Ramage J, et al. Management of neuroendocrine liver metastases. *Am J Surg.* 2004;187:39-46.
20. Dousset B, Houssin D, Soubrane O, et al. Metastatic endocrine tumors: is there a place for liver transplantation? *Liver Transpl Surg.* 1995;1:111-117.
21. Kvols LK. Metastatic carcinoid tumors and the carcinoid syndrome: a selective review of chemotherapy and hormonal therapy. *Am J Med.* 1986;81:49-55.
22. Kvols LK, Buck M. Chemotherapy of endocrine malignancies: a review. *Semin Oncol.* 1987;14:343-353.
23. Moertel CG. Treatment of the carcinoid tumor and the malignant carcinoid syndrome. *J Clin Oncol.* 1983;1:727-740.
24. Moertel CG, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. *J Clin Oncol.* 1989;7:865-868.
25. Engstrom PF, Lavin PT, Moertel CG, et al. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. *J Clin Oncol.* 1984;2:1255-1259.
26. Cheng PN, Saltz LB. Failure to confirm major objective antitumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. *Cancer.* 1999;86:944-948.
27. van Hazel GA, Rubin J, Moertel CG. Treatment of metastatic carcinoid tumor with dactinomycin or dacarbazine. *Cancer Treat Rep.* 1983;67:583-585.
28. Di Bartolomeo M, Bajetta E, Bochicchio AM, et al. A phase II trial of dacarbazine, fluorouracil and epirubicin in patients with neuroendocrine

tumours: a study by the Italian Trials in Medical Oncology (ITMO) Group. *Ann Oncol*. 1995;6:77-79.

29. Faiss S, Pape UF, Bohmig M, et al. Prospective, randomized, multi-center trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors: the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol*. 2003;21:2689-2696.

30. Oberg K. Chemotherapy and biotherapy in neuroendocrine tumors. *Curr Opin Oncol*. 1993;5:110-120.

31. Oberg K, Eriksson B. The role of interferons in the management of carcinoid tumours. *Br J Haematol*. 1991;79(suppl 1):74-77.

32. Oberg K, Norheim I, Lundqvist G, et al. Cytotoxic treatment in patients with malignant carcinoid tumors. Response to streptozocin: alone or in combination with 5-FU. *Acta Oncol*. 1987;26:429-432.

33. Oberg K, Norheim I, Lind E, et al. Treatment of malignant carcinoid tumors with human leukocyte interferon: long-term results. *Cancer Treat Rep*. 1986;70:1297-1304.

34. Oberg K, Norheim I, Alm G. Treatment of malignant carcinoid tumors: a randomized controlled study of streptozocin plus 5-FU and human leukocyte interferon. *Eur J Cancer Clin Oncol*. 1989;25:1475-1479.

35. Oberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with mid-gut carcinoid tumors and carcinoid syndrome. *N Engl J Med*. 1983;309:129-133.

36. Schober C, Schmoll E, Schmoll HJ, et al. Antitumour effect and symptomatic control with interferon alpha 2b in patients with endocrine active tumours. *Eur J Cancer*. 1992;28A:1664-1666.

37. Bajetta E, Zilembo N, Di Bartolomeo M, et al. Treatment of metastatic carcinoids and other neuroendocrine tumors with recombinant interferon-alpha-2a: a study by the Italian Trials in Medical Oncology Group. *Cancer*. 1993;72:3099-3105.

38. Valimaki M, Jarvinen H, Salmela P, et al. Is the treatment of metastatic carcinoid tumor with interferon not as successful as suggested? *Cancer*. 1991;67:547-549.

39. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1980;303:1189-1194.

40. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004;22:4762-4771. Erratum in: *J Clin Oncol*. 2005;23:248.

41. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326:519-523.

42. Ramanathan RK, Cnaan A, Hahn RG, et al. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma: study of the Eastern Cooperative Oncology Group-E6282. *Ann Oncol*. 2001;12:1139-1143.

43. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome: evaluation of a long-acting somatostatin analogue. *N Engl J Med*. 1986;315:663-666.

44. Lamberts SW, van der Lely AJ, de Herder WW, et al. Octreotide. *N Engl J Med*. 1996;334:246-254.

45. Oberg K, Kvols L, Caplin M, et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol*. 2004;15:966-973.

46. Kvols LK, Martin JK, Marsh HM, et al. Rapid reversal of carcinoid crisis with a somatostatin analogue. *N Engl J Med*. 1985;313:1229-1230.

47. Wymenga AN, Eriksson B, Salmela PI, et al. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol*. 1999;17:1111.

48. Saltz L, Trochanowski B, Buckley M, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer*. 1993;72:244-248.

49. Arnold R, Trautmann ME, Creutzfeldt W, et al. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut*. 1996;38:430-438.

50. Arnold R, Wied M, Behr TH. Somatostatin analogues in the treatment of endocrine tumors of the gastrointestinal tract. *Expert Opin Pharmacother*. 2002;3:643-656.

51. 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.

52. 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.

53. Eriksson BK, Larsson EG, Skogseid BM, et al. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer*. 1998;83:2293-2301.

54. 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.

55. Mitty HA, Warner RR, Newman LH, et al. Control of carcinoid syndrome with hepatic artery embolization. *Radiology*. 1985;155:623-626.

56. Perry LJ, Stuart K, Stokes KR, et al. Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. *Surgery*. 1994;116:1111-1117.

57. 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.

58. 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.

59. Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin: evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer*. 1991;68:227-232.

60. Oberg K, Eriksson B. Nuclear medicine in the detection, staging and treatment of gastrointestinal carcinoid tumours. *Best Pract Res Clin Endocrinol Metab*. 2005;19:265-276..