Liver Metastases of Neuroendocrine Tumors: Treatment With Hepatic Transarterial Chemotherapy Using Two Therapeutic Protocols

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OBJECTIVE. The objective of our study was to retrospectively determine the effectiveness of hepatic transarterial chemotherapy using two therapeutic protocols—mitomycin C alone and combined mitomycin C and gemcitabine—on local tumor control and survival rate in patients with liver metastases from neuroendocrine tumors.

MATERIALS AND METHODS. This article describes a retrospective study of 48 patients (age range, 37–77 years; mean age, 61.1 years; SD, 10.3) with liver metastases from neuroendocrine tumors who underwent repetitive selective hepatic artery chemotherapy using mitomycin C alone (group 1, n = 18 patients who underwent 182 therapeutic sessions; mean, 10.11 sessions per patient) and combined mitomycin C and gemcitabine chemotherapy agents (group 2, n = 30 patients who underwent 312 therapeutic sessions; mean, 10.4 sessions per patient) with 4-week intervals between treatment sessions.

RESULTS. Both treatment protocols were well tolerated by all patients. Only minor side effects occurred in both groups, and no major complications developed. Local tumor control evaluation according to the Response Evaluation Criteria in Solid Tumors (RECIST) revealed the following for group 1: partial response, 11.1%; stable disease, 50%; and progressive disease, 38.9%. RECIST criteria for group 2 indicated partial response in 23.33%, stable disease in 53.34%, and progressive disease in 23.33%. The survival rate from the initial diagnosis to the fifth year for group 1 was 11.11% and for group 2, 46.67%. The median survival time from the initial diagnosis of group 1 was 38.67 months, whereas in group 2 it was 57.1 months.

CONCLUSION. Transarterial hepatic chemotherapy using mitomycin C and gemcitabine can be an effective therapeutic protocol for controlling local metastases and improving survival time in patients with hepatic metastases from neuroendocrine tumors.

Keywords: liver metastases, neuroendocrine tumors, oncologic imaging, transarterial chemotherapy

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Neuroendocrine hepatic metastases represent approximately 10% of all hepatic metastatic neoplasms [1]. These metastases occur in 25–90% of patients with neuroendocrine tumors. Metastases from neuroendocrine tumors are a poor prognostic factor for survival and quality of life [2]. Although surgical intervention is the current reference standard curative treatment of patients with liver metastases, nonsurgical alternatives also play an important role in controlling tumor growth and the systemic hormonal effects, particularly in nonsurgical candidates. Tumor-directed methods described in the literature are chemotherapy [3]; biotherapy, including interferon and somatostatin analogs [4]; and transarterial chemoembolization (TACE). TACE is thought to be an effective symptomatic and antiproliferative treatment in patients with progressive disease [2]. An important advantage of TACE is that it has been shown to be a safe technique in high-risk patients. Multiple studies have shown that TACE provides symptomatic control in patients with neuroendocrine metastases [5].

The purpose of this study was to assess and compare the efficacy of local tumor control and the survival times of patients with metastasized neuroendocrine tumors of the liver who were treated with transarterial hepatic chemotherapy using two different therapeutic protocols: mitomycin C alone and mitomycin C combined with gemcitabine as the therapeutic agent. Treatment was followed by transarterial embolization using iodized oil (Lipiodol, Guerbet) and degradable starch microspheres.

Materials and Methods

The medical records of all patients who had histologically proven neuroendocrine tumors with metastasis to the liver between January 1996

and December 2007 were retrospectively evaluated. Approval for this study was obtained from the institutional review board, and informed consent was obtained from all patients. Patient consent included approval of the protocol of treatment and the anonymous use of the results in a research study.

TABLE 1: Characteristics of Patients in Both Groups

Characteristic	Group 1	Group 2
No. of patients	18	30
Sex		
M	13	18
F	5	12
Age (y)		
Range	42–74	37–77
Mean	61.1	59.3
SD	10.6	9.7
No. of patients with primary diagnosis of		
Intestinal neuroendocrine tumor[a]	12	15[a]
Pulmonary tumor	2	2
Pancreatic tumor	2	9
Suprarenal tumor	2	0
Intestinal carcinoid[b]	0	4[b]
No. of patients with		
1 Metastasis	5	8
2 Metastases	2	0
3 Metastases	2	1
Multiple metastases (≥ 5)	9	21
Mean no. of sessions per patient	10.11	10.4
SD	5.95	5.91
Correlation between liver metastases and no. of liver sessions		
1 Liver metastasis		
No. of patients	5	8
No. of sessions	6–8	3–6
2 Liver metastases		
No. of patients	2	0
No. of sessions	6–8	0
3 Liver metastases		
No. of patients	2	1
No. of sessions	6–8	8
≥ 5 Liver metastases		
No. of patients	9	21
No. of sessions	6–24	6–24

[a]Small bowel.
[b]Large intestine.

The current study included 48 patients (age range, 37–77 years; mean age, 61.1 years; SD, 10.3). The inclusion criteria were patients with a liver metastasis or metastases from neuroendocrine tumors, patients without extrahepatic metastases, and those who did not receive concomitant systemic chemotherapy or hormonal therapy. Before intervention, the therapeutic indications were symptomatic treatment in nine patients (18.75%) and palliative therapy in 39 patients (81.25%). Palliative therapy was defined as therapy for asymptomatic patients intended mainly to prolong survival and to preserve and improve quality of life without curing the disease. Symptomatic treatment was defined as a therapy intended to alleviate or decrease tumor-related symptoms (e.g., pain, bulk-related symptoms). The protocol of management was based on the recommendations and government of the institutional oncology board, which includes medical oncologists.

Patient demographics, lesion pathology, treatment, and outcome data, including all histopathology reports and imaging studies, were collected from the electronic medical record archiving system and were subsequently analyzed. In all patients, the diagnosis was made by staff pathologists from our institute based on histologic and immunohistochemical examinations of pathologic specimens. The primary tumor was the source of the biopsy material. For metastases of unknown origin, liver metastases were the source of biopsy material as part of the investigation workup to define the primary cancer.

Information concerning disease-related symptoms, laboratory values, surgical method performed, and adjuvant treatment techniques were obtained from patient reports. Special emphasis was placed on the stage of disease at the time of first embolization: The number of liver tumors and the location and diameter of the largest liver tumor were obtained by reevaluating the original CT and MRI scans. Contraindications to the therapeutic protocol of the study included poor performance status (Karnovsky status ≤ 70%), nutritional impairment, presence of ascites, high serum total bilirubin level (> 3 mg/dL [51.3 μmol/L]), poor hepatic synthesis (serum albumin level < 2.0 mg/dL [20 g/L]), and renal failure (serum creatinine level > 2 mg/dL [176.8 μmol/L]). Partial or complete thrombosis of the main portal vein was a further exclusion criterion for the procedure in addition to cardiovascular or respiratory failure. To ensure adequate treatment compliance, patients were required to have a sound mental state to provide legitimate consent. Nutritional assessment was carried out using the scored patient-generated subjective global assessment, which is one of the standard methods used in many centers for assessing nutritional status in oncology patients [6, 7].

Patients were classified according to the chemotherapeutic drug protocol used in group 1 or group 2. For group 1, mitomycin C was used between January 1996 and December 2001, and for group 2, both mitomycin C and gemcitabine were used between January 2002 and December 2007. The change in the management protocol was based on the recommendations and government of the institutional oncology board, which includes medical oncologists.

TABLE 2: Histopathology and Degree of Pathologic Differentiation of Tumors Involved in the Study in Both Groups

Primary Tumor	Group 1	Group 2
Lung and bronchi	1 Small cell neuroendocrine carcinoma	2 Small cell neuroendocrine carcinomas
	1 Large cell neuroendocrine carcinoma	
Duodenum	1 Well-differentiated tumor	—
Jejunum	2 Undifferentiated tumors	4 Undifferentiated tumors 1 Well-differentiated tumor
Ileum	2 Well-differentiated tumors 3 Undifferentiated tumors	6 Undifferentiated tumors 4 Well-differentiated tumors
Appendix	—	1 Undifferentiated tumor
Cecum	2 Undifferentiated tumors	1 Well-differentiated tumor
Colon	2 Undifferentiated tumors	2 Undifferentiated tumors
Pancreatic (islet cell tumors)	2 Undifferentiated tumors	7 Undifferentiated tumors 2 Well-differentiated tumors
Suprarenal	2 Pheochromocytomas	—

Note—Dash (—) indicates 0 tumors.

Patients included in the study had been referred from oncologists, and the TACE procedure was performed in our center on an outpatient basis. However, the usual practice is to use blocking agents in endocrine-active tumors and hospitalize patients to guard against postembolization hormonal crisis. Observation is performed for 10–12 hours after the procedure including ensuring adequate hydration and symptomatic treatment of pain and vomiting. After the observation time, patients who had remained symptom-free were discharged to the care of the referring oncologist. If complications developed, patients were to be readmitted immediately. The procedure was technically successful and was tolerated by all patients.

Data of Group 1 Patients

Group 1 included 18 patients, 13 men and five women, ranging in age from 42 to 74 years with a mean age of 61.1 years (SD, 10.6). The primary neuroendocrine tumors were as follows: 12 intestinal tumors, two pulmonary tumors, two pancreatic endocrine tumors, and two adrenal tumors. Five patients had one metastasis, two patients had two metastases, two patients had three metastases, and nine patients had multiple metastases (≥ 5 metastases). The patients underwent 182 therapeutic sessions (range, 6–24 sessions; mean, 10.11 sessions; SD, 5.95) using mitomycin C, a chemotherapy drug. The indications for therapy were symptomatic treatment in three patients (16.67%) and palliative treatment in 15 patients (83.33%). Symptoms were either local caused by tumor bulk (right hypochondrial pain or abdominal mass) in or in the form of gastrointestinal tract manifestations including persistent nausea, vomiting, loss of weight, and diarrhea (Tables 1–3).

Data of Group 2 Patients

Group 2 included 30 patients, 18 men and 12 women, ranging in age from 37 to 77 years with a mean age of 59.3 years (SD, 9.7). The primary neuroendocrine tumors were as follows: 15 small-bowel tumors, two pulmonary tumors, nine pancreatic tumors, and four colonic tumors. Eight patients had one metastasis, one patient had three metastases, and 21 patients had multiple metastases (≥ 5 metastases). The patients underwent 312 therapeutic sessions (range, 3–24 sessions; mean, 10.4 sessions; SD, 5.91) using mitomycin C and gemcitabine chemotherapy drugs. The indications for therapy were symptomatic treatment in six patients (20%) and palliative treatment in 24 patients (80%) (Tables 1 and 2).

Resection of the primary tumor was performed in 13 of 18 patients (72.2%) in group 1 and 19 of 30 patients (63.3%) in group 2. All patients in both groups received systemic chemotherapy before chemoembolization. Once the treatment of chemoembolization had been established, no one received adjuvant systemic chemotherapy.

Therapeutic Protocol for Patients

The therapeutic procedures were performed by the same interventionist who had more than 18 years' experience in the field of interventional radiology at the time of the study. After the introduction of a selective catheter through the femoral artery using the Seldinger technique, the localization of the hepatic arteries was confirmed via celiac and mesenteric arteriography using selective catheterization to define the vascular anatomy [8]. Indirect portography was next performed to outline the portal circulation in the venous phase. Subsequently a catheter was placed in the celiac trunk and advanced beyond the gastroduodenal artery. Depending on the size of the tumor, location of the tumor, and arterial supply to the tumor, the tip of the catheter was advanced further into the segmental arteries. The chemotherapeutic agent consisted of mitomycin C alone (8 mg/m^2; mitomycin C, Medac GmbH) for group 1 patients and the combination of mitomycin C (8 mg/m^2) with gemcitabine (1,200 mg/m^2; Gemzar, Lilly Pharma) for group 2 given sequentially and followed by injection of the embolizing materials slowly under fluoroscopic control until stasis of blood flow was observed.

TABLE 3: Response Evaluation Criteria in Solid Tumors (RECIST) Criteria, Survival Rate, and Outcome of Gastrointestinal Tract Versus Pancreatic Tumors in Both Groups

Item	Group 1 (*n* = 18)	Group 2 (*n* = 30)
RECIST criteria, no. (%) of patients		
Partial response	2 (11.1)	7 (23.3)
Stable disease	9 (50)	16 (53.3)
Progressive disease	7 (38.9)	7 (23.3)
Gastrointestinal tumors, no. (%) of patients		
No. of cases	12	19
Partial response	2 (16.7)	5 (26.3)
Stable disease	9 (75)	10 (52.6)
Progressive disease	1 (6.3)	4 (21.1)
Pancreatic tumors, no. (%) of patients		
No. of cases	2	7
Partial response	—	—
Stable disease	—	2 (28.6)
Progressive disease	2 (100)	5 (71.4)
Survival rate from the date of first diagnosis per year (%)		
First year	94.4	100
Second year	77.8	90
Third year	72	80
Fourth year	22.2	63.3
Fifth year	11.1	46.7
Survival time (mo)		
From first diagnosis		
Range	10–68	14–98
Median	38.7	57.1
From first therapy		
Range	5–56	10–72
Median	32.9	42.8
Side effects, no. (%) of patients		
Nausea and vomiting	5 (27.8)	5 (16.7)
Dull aching pain persisting for 24 h	2 (11.1)	3 (10)

Note—Dash (—) indicates 0 cases.

The embolization was performed with a maximum of 15 mL/m^2 of iodized oil (Lipiodol), followed by an injection of 200–450 mg of degradable starch microspheres (EmboCept, PharmaCept) for vessel occlusion. The embolization material was injected slowly with fluoroscopic control until stasis of blood flow was observed. After embolization, devascularization was confirmed with additional angiography of the hepatic arteries. This study was designed to include the performance of at least three sessions of repeated transarterial chemotherapy and embolization, with a treatment interval of 4 weeks. For patients with bilobar disease, the treatment was performed to control disease in the lobe with higher tumor burden as seen on MRI performed immediately before the procedure; the second lobe was treated in another session. The treatment was directed selectively toward the largest lesions (1–3 lesions per session).

The patients were carefully observed after hepatic artery chemotherapy and embolization, and symptoms of postembolization syndrome were treated. The end point of chemotherapy and embolization treatment was defined as stable disease for two successive sessions or disease progression.

Follow-Up and Imaging Analysis

The morphologic tumor response (number, localization, and bulk) was evaluated on MRI in consensus by two senior radiologists with 15 and 8 years' experience. For initial treatment planning, unenhanced and contrast-enhanced MRI was performed. Unenhanced CT was performed 24 hours after embolization to verify that iodized oil had been retained in the tumor and the liver parenchyma, which also reflects the activity of the tumor cells. In addition, CT allows optimal comparison between results on follow-up images in the subsequent sessions and can efficiently exclude major postprocedure complications such as pancreatitis, hepatic infarction, mesenteric ischemia, and ascites or ectopic embolization. CT was performed with the helical technique (section thickness, 8 mm) using CT scanners (Somatom Plus or Somatom Plus 4, Siemens Healthcare). All responses were based on MRI findings. The dimensions of the lesions on follow-up and comparison of those dimensions with the control study dimensions were assessed using MRI owing to its high sensitivity and the high resolution of the images provided.

The volume of the target metastases was measured using transverse imaging to evaluate the longest cross-sectional diameter as the length and the perpendicular diameter as the width. Tumor volume was calculated on the basis of the evaluated diameters on transverse images with the following ellipsoidal volume equation:

$$4/3\pi \times l \times w \times h,$$

where l refers to the length of the tumor; w, the width; and h, the height. The change in size was calculated by radiologic evaluation using MRI. The response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST). Complete response was defined as the complete disappearance of all recognizable tumor in the liver confirmed at 4 weeks after the procedure. Partial response was defined as a reduction of at least 30% in the sum of the longest diameter of the target lesions, taking as reference the baseline study, and was confirmed at 4 weeks. Stable disease was defined when neither partial response nor progressive disease criteria were met, taking as reference the smallest sum of the longest diameter recorded since treatment started. Progressive disease was defined as the appearance of new lesions or as an increase of at least 20% in the sum of the longest diameter of the target lesions, taking as reference the smallest-sum longest diameter recorded since treatment started [9].

Survival times were calculated beginning with the dates of the first TACE treatment and the date of diagnosis of liver metastases using the Kaplan-Meier method [10]. The log-rank test (Cox-Mantel's χ^2 value) was used to determine the significance of the difference between patient survival rates in the two chemotherapy protocol groups. A p value of < 0.05 was considered to be statistically significant.

Results

Technical Details of the Protocol of Treatment, Tolerance, and Side Effects

A dose of 8 mg/m^2 of mitomycin C was given to both groups, whereas a dose of 1,200 mg/m^2 of gemcitabine was given only to group 2. Chemotherapy was given sequentially and was followed by slow injection of embolizing materials under fluoroscopic control until stasis of the blood flow was observed. Embolization was performed with a maximum of 15 mL/m^2 of Lipiodol and was followed by injection of 200–450 mg of EmboCept for vessel occlusion.

Both treatment protocols were well tolerated by all patients, with only minor side effects in both groups and no major complications occurring. Symptomatic improvement was recognized starting from the second therapeutic session in both groups, particularly with regard to right hypochondrial pain, nausea, vomiting, and diarrhea, as well as effort tolerance and quality of life.

The side effects observed in group 1 included nausea and vomiting in five of 18 patients

TABLE 4: MRI Volumetric Changes of Tumors After Transarterial Chemotherapy in Both Groups

MRI Finding	Group 1	Group 2
Tumor volume (mL)		
Before transarterial chemotherapy		
Mean	9.2	12.4
Range	4.0–68.6	6.2–72.6
Longest axial diameter of tumor (mm)		
Mean	27.1	3.8
Range	5–46	4–72
SD	10.2	10.6
Tumor volume (mL)		
3 mo after therapy		
Mean	8.9	9.14
Range	3.2–62.6	4.8–68.6
6 mo after therapy		
Mean	8.72	8.2
Range	2.2–66.6	4.2–62.6
9 mo after therapy		
Mean	9.3	7.1
Range	2.1–64.8	4.1–61.9
12 mo after therapy		
Mean	10.6	7.2
Range	3.4–72.6	3.4–64.6

(27.8%) and a dull aching upper abdominal pain persisting for 24 hours in two of 18 patients (11.1%). In group 2, five of 30 (16.7%) patients experienced nausea and vomiting, and dull aching upper abdominal pain persisting for 24 hours occurred in three patients (10%). No patients had biliary obstruction.

MRI Findings

Local tumor morphologic evaluations according to RECIST criteria were as follows for group 1 (n = 18): partial response in two patients (11.1%), stable disease in nine patients (50%), and progressive disease in seven patients (38.9%). For group 2 (n = 30), partial response was seen in seven patients (23.3%), stable disease in 16 patients (53.3%), and progressive disease in seven patients (23.3%). Tumor response according to RECIST criteria was compared between gastrointestinal tract tumors versus pancreatic tumors (Tables 3 and 4).

MRI volumetric response of tumor load to the treatment protocol of both groups revealed progressive reduction of the mean tumor volumes over a 3-month follow-up interval in comparison to the pretherapeutic mean tumor volume in group 1 patients. Comparatively the initial reduction in the mean tumor volume in the first 6 months was followed by progressive increase afterward in group 2. Volumetric results are summarized in Table 4. However, the mean volumetric changes between pre- and posttreatment tumor volumes were not statistically significant for group 1 or group 2, with a p value of 0.09 and 0.06, respectively (Table 3 and Fig. 1).

Correlation Between Tumor Response and Iodized Oil Uptake on Unenhanced CT

In both groups, metastases with heterogeneous Lipiodol uptake tended to progress more frequently (60%; p = 0.04) than those with homogeneous uptake (24%; p = 0.1) in which metastases revealed stable disease and partial response.

Survival Analysis and Extrahepatic Progression

The survival rates, which were calculated from the time of first diagnosis, from the first year until the fifth year in group 1 were as the follows: 94.4% in the first year, 77.78% in the second year, 72% in the third year, 22.2% in the fourth year, and 11.1% in the fifth year. The survival rates in group 2 were 100% in the first year, 90% in the second year, 80% in the third year, 63.3% in the fourth year, and 46.7% in the fifth year (Table 3, Figs. 2 and 3).

The median survival time of group 1 starting from the first diagnosis was 38.7 months, (range, 10–68 months), whereas the median survival time of the same group starting from the first transarterial chemotherapy session was 32.9 months (range, 5–56 months). In group 2 the median survival time starting from the first diagnosis was 57.1 months (range, 14–98 months), and the median survival time starting from the first TACE session was 42.8 months (range, 10–72 months). The time lapse between the diagnosis and first treatment of group 1 was 5–9 months and for group 2, 4–12 months. A significant difference in the survival rates, which were calculated from the date of first diagnosis and first TACE session of both patient groups, was detected for both groups on analysis by log-rank test (Cox-Mantel's χ^2 method), with a p value of 0.001 and 0.005, respectively.

Resection of the primary tumor was performed in 13 of 18 patients (72.2%) in group 1 and 19 of 30 patients (63.3%) in group 2.

The mean time of extrahepatic progression in group 1 was 10.2 months (SD, 2.3), whereas in group 2 the mean progression time was 16.4 months (SD, 4.2).

Discussion

The presence and extension of hepatic metastases are considered to be among the most important prognostic factors for patients with neuroendocrine tumors. These factors significantly impair a patient's quality of life as a result of the symptoms caused by endocrine tumor products. Effective treatment of liver metastases is crucial to maintain optimal palliative treatment of patients with advanced neuroendocrine tumors because only 5% of patients with carcinoid syndrome undergo complete radical liver surgery [11]. Multimodality treatment protocols, including surgery of the primary tumor and metastases, TACE, and adjuvant pharmacologic treatment (bioimmunotherapy and chemotherapy), have been established for the treatment of metastatic gastrointestinal neuroendocrine tumors [12–14]. Symptomatic patients may benefit from TACE in terms of improved quality of life or reduced dose of somatostatin analog. Radiofrequency ablation has also been applied for the treatment of hepatic metastases resulting from neuroendocrine tumors in many series in the literature [15–18].

According to the RECIST criteria of tumor morphologic changes used in both patient groups, there was an improved response in group 2 patients versus group 1 patients regarding tumor regression, tumor course stability, and tumor progression. We attribute these differences in response to the synergistic and cumulative effects of both mitomycin C and gemcitabine on tumor activity. This potentiating effect of the combination of mitomycin C and gemcitabine was also reflected in the median survival time of group 2 patients. The response of gastrointestinal tract tumors was more favorable than that of pancreatic tumors in both groups.

Seldinger [6] reported a median survival time of 24 months in 23 patients after the initial TACE using Adriamycin and Lipiodol. In a study of eight patients with carcinoid tumors, Hajarizadeh et al. [19] reported a mean survival time of 40 months from the initial diagnosis with chemoembolization using a mixture of doxorubicin, cisplatin, mitomycin C, and Lipiodol. In their study of 18 patients with liver metastases from neuroendocrine tumors, Touzios et al. [5] followed up on the results of TACE therapy using a protocol of combined cisplatin, doxorubicin, and mitomycin C. The median and 5-year survival rates were 50 months and 50%, respectively. Ruutiainen et al. [20] used a protocol of cisplatin, doxorubicin, mitomycin C, iodized oil, and polyvinyl alcohol. The survival rates at 1, 3, and 5 years after therapy were 86%, 67%, and 50%, respectively. They also reported that severe toxicity after chemoembolization was seen in 25% of cases, possibly because of the combination of multiple chemotherapeutic agents used simultaneously. Loewe et al. [21] described the effect of permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and Lipiodol on the short- and long-term results. The median survival time reported in that study was 69 months, and the estimated cumulative survival rates reached 95.7% and 65.4% at 1 and 5 years after diagnosis, respectively. Permanent arterial embolization, however, carries a technical disadvantage in that another intervention might not be technically feasible after the permanent embolization of all hepatic arteries. They also reported major complications after this protocol including two deaths (8.7%) that occurred within 1 month of treatment and a vascular complication that occurred at the time of embolization [21].

In comparison with the data for TACE reported in the literature, the effect on survival rates achieved by the treatment protocols used in this study, particularly that used for group 2 patients, appears to be favorable,

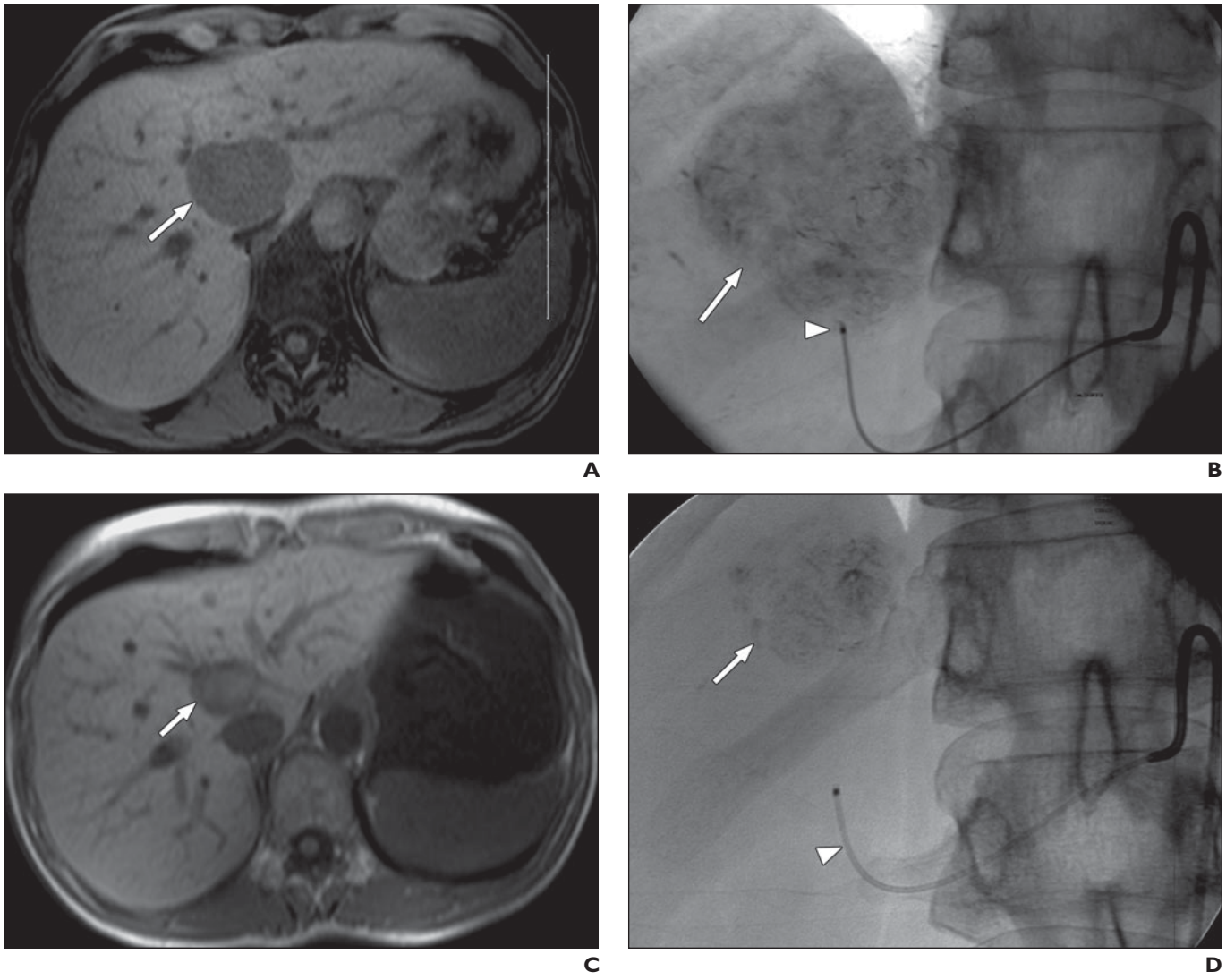

Fig. 1—46-year-old woman (patient from group 2) with neuroendocrine carcinoma.
A, Axial MRI scan shows metastatic liver lesion (*arrow*) from undifferentiated colonic neuroendocrine carcinoma.
B, Axial MRI scan obtained after first embolization session shows liver uptake of iodized oil (Lipiodol, Guerbet) (*arrow*). Also note tip of microcatheter in artery is supplying tumor (*arrowhead*).
C, Axial MRI scan obtained after third embolization shows more than 50% reduction in size of tumor (*arrow*), which is representative of partial response.
D, Image obtained after third embolization session shows reduction in tumor uptake of Lipiodol (*arrow*). Tip of microcatheter can be seen in vessel supplying tumor (*arrowhead*).

although the number of therapeutic sessions needed was relatively higher. This study used only one or two chemotherapeutic agents to strike a balance between the increased synergistic therapeutic effects of the chemotherapeutic agents and minimization of the toxic side effects from the use of multiple therapeutic agents.

In this study, patients with tumors that had heterogeneous Lipiodol uptake on CT had a higher tendency to show progressive disease during the follow-up period than those with tumors that had homogeneous uptake in both groups. These results are in accordance with other results shown by the effect of TACE on other tumors including hepatocellular carcinoma [22].

A recent study by de Baere et al. [23] emphasized the effect of drug-eluting beads loaded with doxorubicin on progressive liver metastases from well-differentiated gastroenteropancreatic endocrine tumors in 20 patients. Partial response, stable disease, and progressive disease achieved on 3-month follow-up were 80%, 15%, and 5%, respectively. The median time to progression was 15 months. However, complications reported include postembolization syndrome in 67% of the patients and TACE-induced peripheral liver necrosis in 25% [23].

A limitation of our study is the retrospective study design; however, because of the slow growth and the relatively low incidence rate of neuroendocrine carcinomas, inclusion of a large study population from a single institution of prospective fashion would be difficult. Another limitation is the unequal number of patients in groups 1 and 2.

In conclusion, the dual regimen of gemcitabine and mitomycin C is superior to mitomycin C alone and provides an effective treatment of the hepatic metastases resulting

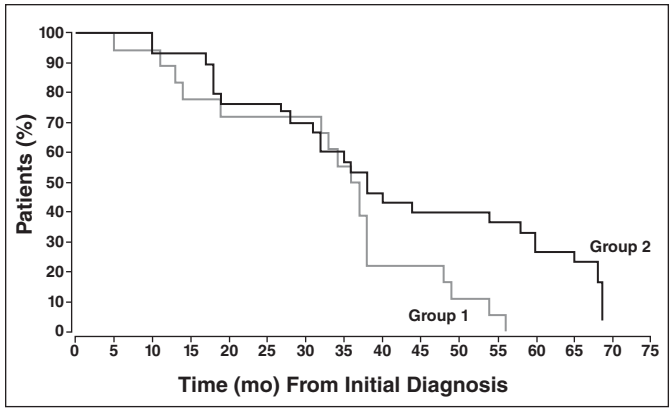

Fig. 2—Kaplan-Meier survival curve for both groups from initial diagnosis. Group 1 patients (n = 18) were treated using transarterial chemotherapy with mitomycin C. Median survival rate was 38.67 months (range, 10–68 months). Group 2 patients (n = 30) were treated using transarterial chemotherapy with combination of mitomycin C and gemcitabine. Median survival rate of group 2 was 57.1 months (range, 14–98 months).

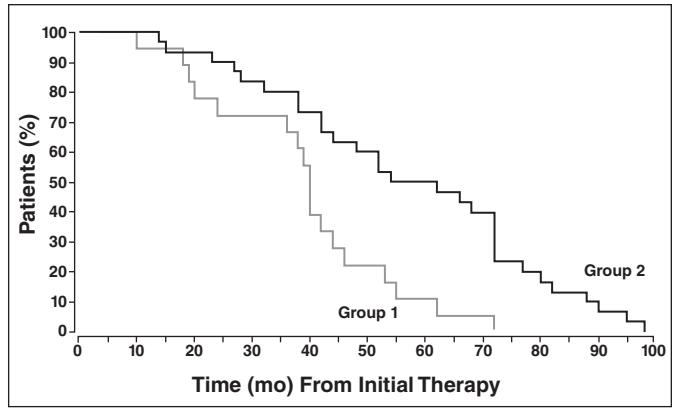

Fig. 3—Kaplan-Meier survival curve for both groups from initial therapy. Group 1 patients (n = 18) were treated using transarterial chemotherapy with mitomycin C. Median survival rate was 32.89 months (range, 5–56 months). Group 2 patients (n = 30) were treated using transarterial chemotherapy with combination of mitomycin C and gemcitabine. Median survival rate of group 2 was 42.8 months (range, 10–72 months).

from neuroendocrine tumors. The procedure yields an adequate response rate and, when repeated periodically, maintains clinical remissions for extended periods of time.

References

1. Benevento A, Boni L, Frediani L, Ferrari A, Dionigi R. Result of liver resection as treatment for metastases from noncolorectal cancer. *J Surg Oncol* 2000; 74:24–29
2. Kress O, Wagner HJ, Wied M, Klose KJ, Arnold R, Alfke H. Transarterial chemoembolization of advanced liver metastases of neuroendocrine tumors: a retrospective single-center analysis. *Digestion* 2003; 68:94–101
3. Oberg K. Chemotherapy and biotherapy in neuroendocrine tumours. *Curr Opin Oncol* 1993; 5:110–120
4. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome: evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986; 315:663–666
5. Touzios JG, Kiely JM, Pitt SC, et al. Neuroendocrine hepatic metastases: does aggressive management improve survival? *Ann Surg* 2005; 241:776–783
6. Seldinger SI. Catheter replacement of needle in percutaneous arteriography: a new technique. *Acta Radiol* 1953; 39:368–372
7. Read JA, Crockett N, Volker DH, et al. Nutritional assessment in cancer: comparing the Mini-Nutritional Assessment (MNA) with the scored Patient-Generated Subjective Global Assessment (PGSGA). *Nutr Cancer* 2005; 53:51–56
8. Read JA, Choy ST, Beale PJ, Clarke SJ. Evaluation of nutritional and inflammatory status of advanced colorectal cancer patients and its correlation with survival. *Nutr Cancer* 2006; 55:78–85
9. Padhani AR, Ollivier L. The RECIST (Response Evaluation Criteria in Solid Tumors) criteria: implications for diagnostic radiologists. *Br J Radiol* 2001; 74:983–986
10. Kaplan EL, Meier P. Non parametric estimation from incomplete observation. *J Am Stat Assoc* 1958; 53:457–481
11. Neary PC, Redmond PH, Houghton T, Watson GR, Bouchier-Hayes D. Carcinoid disease: review of the literature. *Dis Colon Rectum* 1997; 40:349–362
12. Therasse E, Breittmayer F, Roche A, et al. Transcatheter chemoembolization of progressive carcinoid liver metastasis. *Radiology* 1993; 189:541–547
13. Tancredi T, McCuskey PA, Kan Z, Wallace S. Changes in rat liver microcirculation after experimental hepatic arterial embolization: comparison of different embolic agents. *Radiology* 1999; 211: 177–181
14. Brown KT, Koh BY, Brody LA, et al. Particle embolization of hepatic neuroendocrine metastases for control of pain and hormonal symptoms. *J Vasc Interv Radiol* 1999; 10:397–403
15. 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
16. Henn AR, Levine EA, McNulty W, et al. Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes. *AJR* 2003; 181:1005–1010
17. Elvin A, Skogseid B, Hellman P. Radiofrequency ablation of neuroendocrine liver metastases. *Abdom Imaging* 2005; 30:427–434
18. Gillams A, Cassoni A, Conway G, et al. Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. *Abdom Imaging* 2005; 30:435–441
19. Hajarizadeh H, Ivancev K, Mueller CR, Fletcher WS, Woltering EA. Effective palliative treatment of metastatic carcinoid tumors with intra-arterial chemotherapy/chemoembolization combined with octreotide acetate. *Am J Surg* 1992; 163: 479–483
20. Ruutiainen 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
21. Loewe C, Schindl M, Cejna M, Niederle B, Lammer J, Thurnher S. Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and Lipiodol: assessment of mid- and long-term results. *AJR* 2003; 180:1379–1384
22. Nishimine K, Uchida H, Matsuo N, et al. Segmental transarterial chemoembolization with Lipiodol mixed with anticancer drugs for nonresectable hepatocellular carcinoma: follow-up CT and therapeutic results. *Cancer Chemother Pharmacol* 1994; 33[suppl]:S60–S68
23. de Baere T, Deschamps F, Teriitheau C, et al. Transarterial chemoembolization of liver metastases from well differentiated gastroenteropancreatic endocrine tumors with doxorubicin-eluting beads: preliminary results. *J Vasc Interv Radiol* 2008; 19: 855–861