Chemoembolization and Bland Embolization of Neuroendocrine Tumor Metastases to the Liver

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PURPOSE: To assess the toxicity and efficacy of chemoembolization and bland embolization in patients with neuroendocrine tumor metastases to the liver.

MATERIALS AND METHODS: A total of 67 patients underwent 219 embolization procedures: 23 patients received primarily bland embolization with PVA with or without iodized oil and 44 primarily received chemoembolization with cisplatin, doxorubicin, mitomycin-C, iodized oil, and polyvinyl alcohol. Clinical, laboratory, and imaging follow-up was performed 1 month after completion of therapy and every 3 months thereafter. Patients with disease relapse were treated again when feasible. Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0. Efficacy was assessed by clinical and morphologic response. Time to progression (TTP), time to treatment failure, and survival were estimated by Kaplan–Meier analysis.

RESULTS: Ten of 67 patients (15%) were lost to follow-up. The mortality rate at 30 days was 1.4%. Toxicities of grade 3 or worse in severity occurred after 25% of chemoembolization procedures and 22% of bland embolization procedures (odds ratio, 1.2; 95% CI, 0.4–4.0). Mean length of stay was 1.5 day in both groups. Rates of freedom from progression at 1, 2, and 3 years were 49%, 49%, and 35% after chemoembolization and 0%, 0%, and 0% after bland embolization (log-rank test, $P = .16$). Among the subgroup with carcinoid tumors, the proportions without progression were 65%, 65%, and 52% after chemoembolization and 0%, 0%, and 0% after bland embolization (log-rank test, $P = .08$). Patients treated with chemoembolization and bland embolization experienced symptomatic relief for means of 15 and 7.5 months, respectively ($P = .14$). Survival rates at 1, 3, and 5 years after therapy were 86%, 67%, and 50%, respectively, after chemoembolization and 68%, 46%, and 33%, respectively, after bland embolization (log-rank test, $P = .18$).

CONCLUSIONS: Chemoembolization was not associated with a higher degree of toxicity than bland embolization. Chemoembolization demonstrated trends toward improvement in TTP, symptom control, and survival. Based on these results, a multicenter prospective randomized trial is warranted.

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Abbreviations: NET = neuroendocrine tumor, TTP = time to progression, TTTF = time to treatment failure

NEUROENDOCRINE tumors (NETs) are malignant growths of cells arising from various endocrine organs throughout the body. They are believed to originate from a precursor cell population that shares antigens with neural and endocrine tissues (1). Many NETs retain their ability to secrete biologically active substances, the identity of which is determined by the tissue type of the primary tumor. The release of these factors is the cause of significant morbidity and mortality, triggering symptoms such as hypoglycemia (ie, insulinomas), Zollinger-Ellison Syndrome (ie, gastrinomas), and carcinoid heart disease (ie, carcinoid tumors) (1,2). Nevertheless, most well differentiated NETs are fairly benign, often growing insidiously for years before demonstrating overt symptoms.

NETs are generally divided between those that originate from the

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gastrointestinal tract or lungs—termed carcinoid tumors—and those derived from other tissues, most notably from pancreatic islet cells (1). Carcinoid NETs are a diverse group of tumors that were initially believed to be more indolent than gastrointestinal adenocarcinomas; nevertheless, one large study (3) showed that these tumors have considerable malignant potential, with 45.3% of patients having developed metastases by the time of initial diagnosis. Because 74% of carcinoid NETs arise in the gastrointestinal tract, the liver is a natural site for metastatic growth (3). This is true for noncarcinoid NETs as well, although this subgroup represents an even more heterogeneous assembly of tumors, with considerable variability in natural histories (1).

The establishment of distant metastases is associated with a poor prognosis for neuroendocrine tumors: patients with carcinoid NETs have a 5-year survival rate of only 22% from this event (3). Therefore, considerable attention has focused on the treatment of liver metastases. Therapeutic options include systemic chemotherapy, radiation therapy, surgical resection, and liver transplantation (1,4). When excessive tumor bulk or other biologically unfavorable features preclude these options, other treatment modalities have been employed (5). Particularly, because NET metastases derive their principal blood supply from the hepatic artery, it is possible to trigger selective ischemic necrosis of these growths by occlusion of their arterial supply (6). This tactic has been employed by surgical ligation and transarterial embolization of the hepatic artery (6).

Hypothetically, the addition of chemotherapeutic agents to embolic therapy could increase tumor response rates compared with bland embolization (7). The efficacy of such chemoembolization of NET liver metastases (1) has already been displayed by various small studies with samples of five to 30 patients (8–14). Nevertheless, it remains unclear whether chemoembolization of NETs is superior to conventional bland embolization. For example, one study of 41 patients (15) demonstrated a 50% response rate with use of bland embolic therapy, which is on par with the findings of many chemoembolization experiments (1). Moreover, because of the use of cytotoxic agents, a priori hypotheses have suggested that chemoembolization might result in a higher incidence of treatment-related toxicities than bland embolic therapy (16). However, proof of such an assertion has not been well demonstrated.

MATERIALS AND METHODS

Institutional review board exemption was obtained for this retrospective review. A total of 67 patients were treated in the interventional radiology clinic between 1991 and 2005 with liver metastases from neuroendocrine tumors; 30 (45%) were men and 37 (55%) were women. Their primary tumors included 38 carcinoid NETs (57%), 14 pancreatic islet-cell tumors (21%), four gastrinomas (6%), three other NETs (4%; VIPoma, pecoma, and medullary thyroid carcinoma in one case each), and eight uncharacterized neuroendocrine tumors (12%). A total of 69% of all tumors were found to be hormonally active. The patients were initially diagnosed at an average age of 52 years (range, 20–83 y) and developed liver metastases an average of 2 years later.

Before undergoing embolic therapy, 29 patients (43%) underwent surgical resection of their primary tumors and five (7%) underwent partial hepatectomy for treatment of metastases. Forty individuals (60%) underwent some form of chemotherapy and seven (10%) were treated with radiation therapy.

Patients underwent initial embolization an average of 31 months after the diagnosis of liver metastases (range, 0–298 months). For purposes of survival analysis, the patients were classified as having undergone bland embolization or chemoembolization based on the predominant therapy administered. Overall, the chemoembolization group included 44 patients (65% of the total), of whom eight (18%) received some bland embolic treatments; the bland embolization group included 23 patients (34% of the total), of whom two (9%) received some chemoembolization treatments. Crossover patients were predominantly assigned to the chemoembolization arm because, in clinical practice, they typically received chemoembolization to prolong the treatment response achieved by bland embolization; moreover, their inclusion in the experimental arm was expected to cause any skew in the data to be toward the null hypothesis. The two crossover subjects in the bland embolization group were included because their therapy was overwhelmingly conducted by this modality (10 bland embolization procedures vs three chemoembolization procedures and eight bland embolization procedures vs two chemoembolization procedures, respectively).

All patients underwent preprocedural diagnostic cross-sectional imaging to assess tumor burden: 58 (87%) had three or more liver metastases. An average of two embolization procedures (range, 1–4) were performed during the initial cycle. Because 45% of the patients were eventually treated again after their initial cycle, they ultimately underwent an average of 3.3 total embolization treatments (range, 1–13). Chemoembolization was performed according to standard protocol at our institution as summarized elsewhere (17). Bland embolization was performed with 150–250-μm granular polyvinyl alcohol particles (Contour; Boston Scientific, Natick, MA) with or without the addition of iodized oil (Ethiodol; Savage Laboratories, Melville, NY). The choice of treatment was at the discretion of the attending interventional oncologist. Endpoints for embolization were similar in the two groups, with a goal of a "tree-in-winter" or "pruned-tree" appearance with preservation of flow in the segmental hepatic arteries.

Treatment toxicity was assessed by the length of inpatient hospital stay and by quantitative grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (18). These toxicity data were gathered from hospital discharge summaries, nurses' notes, and hospital records. Student t tests were used to test for statistically significant differences between patients treated with chemoembolization versus bland embolization.

Procedural efficacy was monitored by follow-up cross-sectional imaging scheduled for 1 month after completion of the initial embolization cycle. Comparison of pre- and posttreatment images was used to determine tumor status, whereby it was classified to be in regression, stabilization, or progres-

Table 1
Procedural Toxicities of Chemoembolization According to CTCAE Version 3.0 (%)

Toxicity Grade	Pain	Fever	Nausea	Vomiting	Fatigue	Weight Loss	Bilirubin	GGT/ ALP	AST	ALT	Infection	Cardiac	Other
1	70	21	53	31	6	12	0	18	1	1	3	7	11
2	18	1	3	1	4	1	1	9	1	1	3	3	6
3	3	0	1	1	0	0	0	4	1	0	1	0	1
4	0	0	0	0	0	0	0	0	0	1	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0
Total ± 95% CI	91 ± 16	22 ± 7	57 ± 14	34 ± 9	9 ± 3	14 ± 5	1 ± 1	30 ± 7	3 ± 2	2 ± 2	6 ± 3	10 ± 4	18 ± 5

Note.—ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transpeptidase.

Table 2
Procedural Toxicities of Bland Embolization According to CTCAE Version 3.0 (%)

Toxicity Grade	Pain	Fever	Nausea	Vomiting	Fatigue	Weight Loss	Bilirubin	GGT/ ALP	AST	ALT	Infection	Cardiac	Other
1	46	11	33	24	11	8	0	16	0	0	0	3	6
2	19	0	5	4	0	3	0	5	0	0	1	6	8
3	0	0	0	0	0	0	0	3	1	0	0	1	1
4	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	1
Total ± 95% CI	65 ± 18	11 ± 7	38 ± 15	28 ± 11	11 ± 6	10 ± 5	0	24 ± 9	1 ± 2	0	1 ± 2	10 ± 5	16 ± 7

Note.—ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transpeptidase.

sion according to the Response Evaluation Criteria in Solid Tumors (19). Patients whose tumors stabilized who had a particularly large tumor burden and all patients with tumor progression were reevaluated for additional embolization; another cycle was performed when clinically appropriate. Patients whose disease was in regression were followed by repeat imaging every 3 months; in the event of a relapse, another cycle of embolic therapy was offered whenever possible. Clinical response was assessed by patients' self-reported hormone-related symptoms.

Kaplan-Meier survivorship curves were generated with MedCalc software (version 8.1.0.0; MedCalc, Mariakerke, Belgium) from diagnosis of the primary tumor and liver metastases and the time of initial treatment. Patients who exhibited morphologic stabilization or regression were monitored for time to progression (TTP; ie, time to tumor progression) and time to treatment failure (TTTF). TTP was defined as the time from initial stabilization to the first examination with radiographic progression; those patients whose disease never exhibited stabilization or regression were classified as having a TTP of 0 months. TTTF was defined as the time from initial stabilization to the first progression after the last successful cycle of therapy. Kaplan-Meier curves were generated from these data to account for loss to follow-up. Separate survival and TTP curves were generated for various subgroups based on tumor type, hormonal activity, presence of extrahepatic disease, and type of therapy.

RESULTS

The patient populations in the two treatment groups were statistically identical: there were no significant differences in the proportion of patients with carcinoid NETs (chemoembolization, 50%; bland embolization, 65%), hormonally active tumors (68% and 70%, respectively), documented extrahepatic metastases (23% and 30%), or history of attempted tumor resection (48% and 43%). There were no differences in pretreatment liver function as assessed by bilirubin levels ($P = .77$) or albumin levels ($P = .28$). Performance status was also identical between groups.

The 30-day mortality rate for both procedures was 1.4% (three deaths among 219 embolization procedures). Two of these patients were treated with bland embolization and one was treated with chemoembolization. All had presented with advanced tumor burden and deteriorated performance status.

Toxicities were graded according to CTCAE version 3.0 criteria (18) for each embolization procedure for pain, fever, nausea, vomiting, fatigue, weight loss, increases in serum aminotransferase and alkaline phosphatase levels, infection, cardiac complications, and any other recorded toxicities.

Although the incidence of some degree of postembolization syndrome was quite high, these symptoms were generally well controlled and self-limited (**Tables 1, 2**; **Fig 1**). Severe toxicities (CTCAE grade ≥3) occurred in 11 of 44 chemoembolization procedures (25%) and five of 23 bland emboliza-

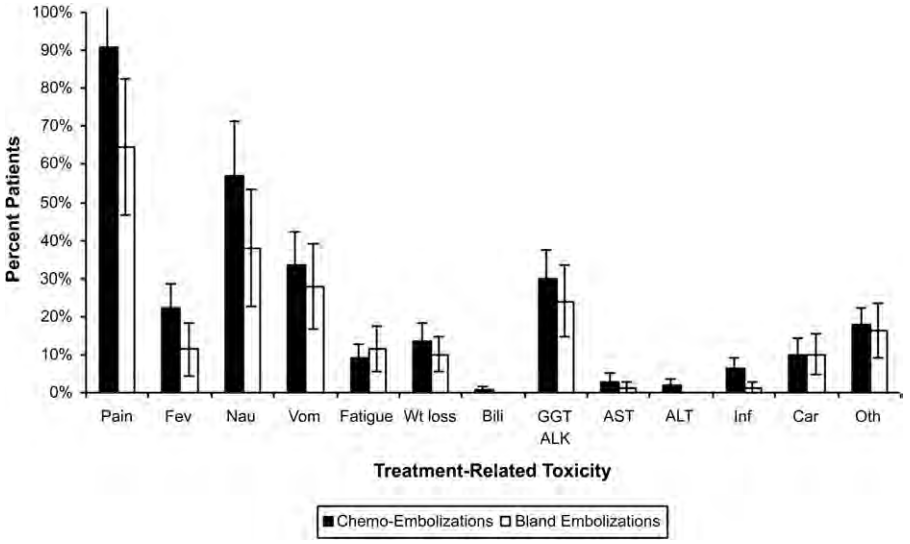

Figure 1. Embolization-related toxicities according to CTCAE version 3.0 criteria.

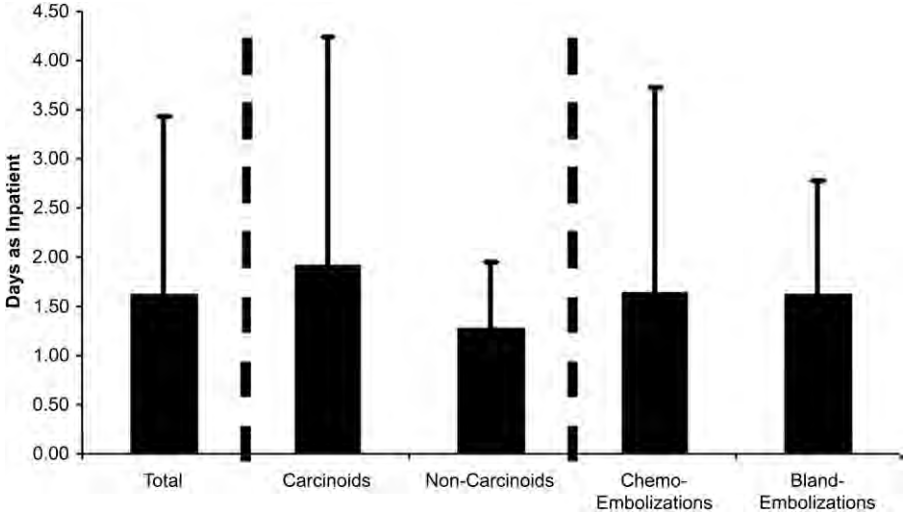

Figure 2. Average hospital stay per embolization procedure.

tion procedures (22%; odds ratio, 1.2; 95% CI, 0.4–4.0). The only significant difference among toxicities of any grade was an increased incidence of infections among patients in the chemoembolization group ($P = 0.01$). This may be related to the greater prevalence of a bilioenteric anastomosis or stent in the chemoembolization group, although the numbers are too small for statistical comparison. Nevertheless, infection was rare (6%), mild, and self-limited; only 1% of the patients experienced an infection of grade 3 or greater.

There were no significant differences in length of hospital stay between patients treated with chemoembolization and bland embolization or between those with carcinoid and noncarcinoid tumors. Patients in all groups were kept in the ward for an average of 1.5 days. A few outliers did occur, such as one patient who was hospitalized for 18 days (**Fig 2**).

The initial efficacy of the treatments was evaluated by comparison of cross-sectional imaging 1 month after the completion of the initial cycle of embolization with a pretreatment baseline for each patient. Although the proportion of patients whose tumors progressed was similar among those who received bland embolization (13%) and chemoembolization (12%), those who were treated with chemoembolization were modestly more likely to exhibit tumor regression: 66% versus 50% among patients who received bland embolization (odds ratio, 1.9; 95% CI, 0.6–6.2; **Fig 3**). A total of 38% of patients who received bland embolization and 22% of those who received chemoembolization exhibited disease stabilization according to Response Evaluation Criteria In Solid Tumors.

The TTP was dramatically shorter for patients who received bland embolization than for those who were treated with chemoembolization (**Fig 4**). The percentages of patients free of radiologic progression at 6, 12, 24, and 36 months were 65%, 49%, 49%, and 35%, respectively, among patients who received chemoembolization and 73%, 0%, 0%, and 0%, respectively, among patients who received bland embolization, with median TTPs of 12 and 6 months, respectively. However, because this difference emerged only after 50% of patients had shown disease progression, this finding failed to achieve statistical significance (log-rank test, $P = .16$). This suggested that some subgroup of patients disproportionately benefited from chemoembolization. The trend of increased TTP among patients who received chemoembolization was further amplified among patients with carcinoid tumors (log-rank test, $P = .08$) compared with those with noncarcinoid cancers (log rank test, $P = .82$; **Fig 5**). Because only 20 patients had carcinoid tumors treated with chemoembolization, this study lacked the statistical power to resolve this difference.

However, an alternative phrasing of this finding achieves statistical significance: given the diagnosis of a carcinoid tumor, the TTP of the patient is considerably better if (s)he receives chemoembolization rather than bland embolization ($P = .01$; **Fig 6**). The proportions of patients with carcinoid NETs without progression at 6, 12, 24, and 36 months were 78%, 65%, 65%, and 52%, respectively, in patients who received chemoembolization and 69%, 0%, 0%, and 0%, respectively, in patients who received bland embolization, with median TTPs of 55 and 10 months, respectively. Again, this difference fails to emerge among patients with noncarcinoid tumors: patients treated with chemoembolization and

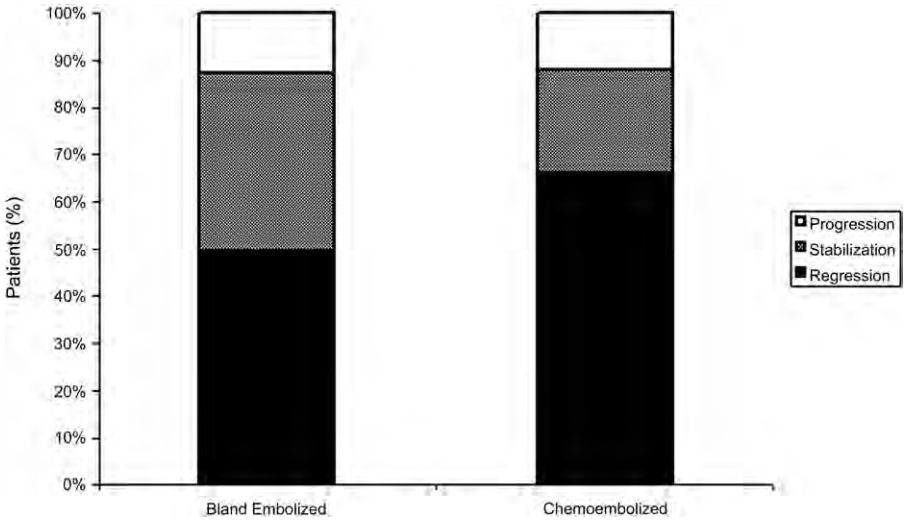

Figure 3. Tumor status 1 month after initial embolization.

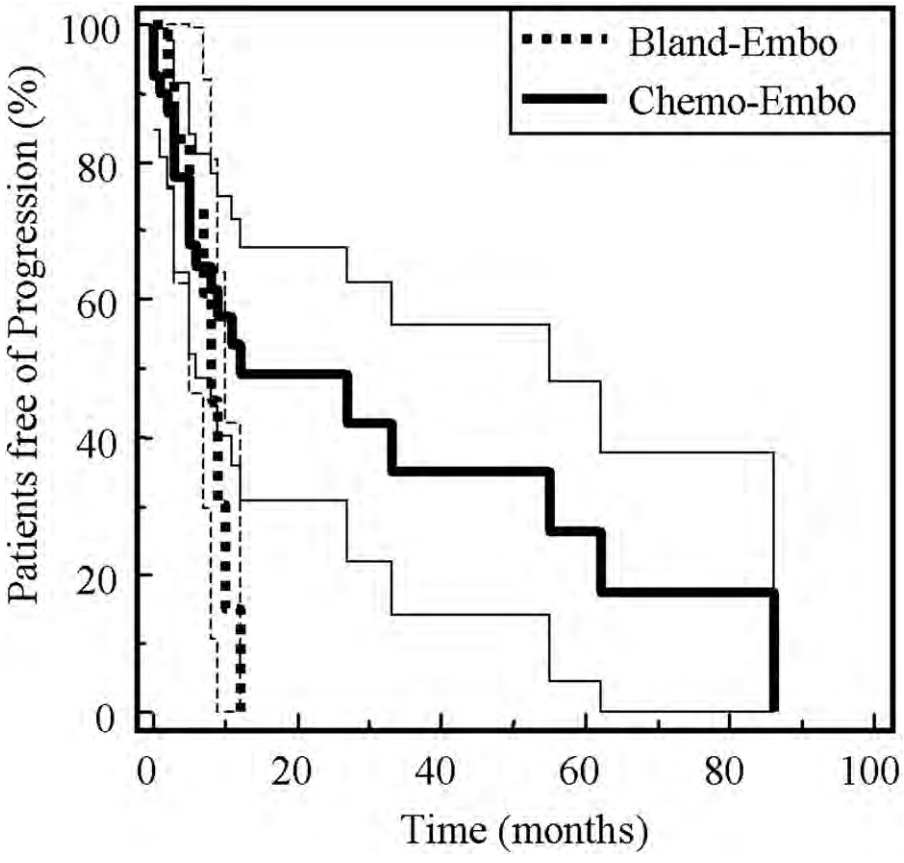

Figure 4. TTP after initial embolization in all patients.

bland embolization patients have median TTPs of 5 and 8 months, respectively.

Despite the differences between chemoembolization and bland embolization in terms of TTP, no such differences were found for TTTF at 6, 12, 24, and 36 months: 74%, 71%, 65%, and 47%, respectively, among patients who received chemoembolization and 73%, 46%, 46%, and 46%, respectively, among those who received bland embolization ($P = 0.86$). There was also no significant difference in median TTTF: 33 months among patients who received chemoembolization versus and 8 months for those who received bland embolization. Therefore, the present study lacks the statistical power to determine whether a true difference exists between treatment arms in terms of TTTF.

A major goal of embolic therapy in addition to slowing of tumor progression is palliation of symptoms. Both treatment groups experienced similar rates of symptomatic relief: 92% in the chemoembolization group and 93% in the bland embolization group experienced an improvement in their symptoms. This improvement lasted a mean of 15 months for patients who received chemoembolization and 7.5 months for those who received bland embolization. However, the considerable range of response times in both groups kept this result from attaining statistical significance ($P = .14$).

Finally, in terms of overall survival after initial embolic treatment, chemoembolized patients had a median life expectancy of 44 months, compared with 39 months among those who received bland embolization; in these groups, survival rates at 1, 2, 5, and 10 years were 86%, 69%, 49%, and 49%, respectively, in the chemoembolization group; and 64%, 59%, 39%, and 17%, respectively, in the bland embolization group. Although a trend favoring patients who received chemoembolization had begun to emerge, especially among longer-term survivors, our study lacked the statistical power to resolve any differences between the treatment groups (log-rank test, $P = .18$; **Fig 7**). Moreover, patients with carcinoid tumors who were treated with chemoembolization showed a nonsignificant trend toward slightly better survival from their first embolic treatment compared with those who received bland embolization, with median survival times of 128 and 60 months, respectively, and 1-, 2-, 5-, and 10-year survival rates of 95%, 78%, 61%, and 61%, respectively, among those who received chemoembolization and 71%, 71%, 38%, and 38%, respectively, among those who received bland embolization ($P = .49$). The longer absolute survival times among patients with carcinoid NETs, regardless of embolization treatment,

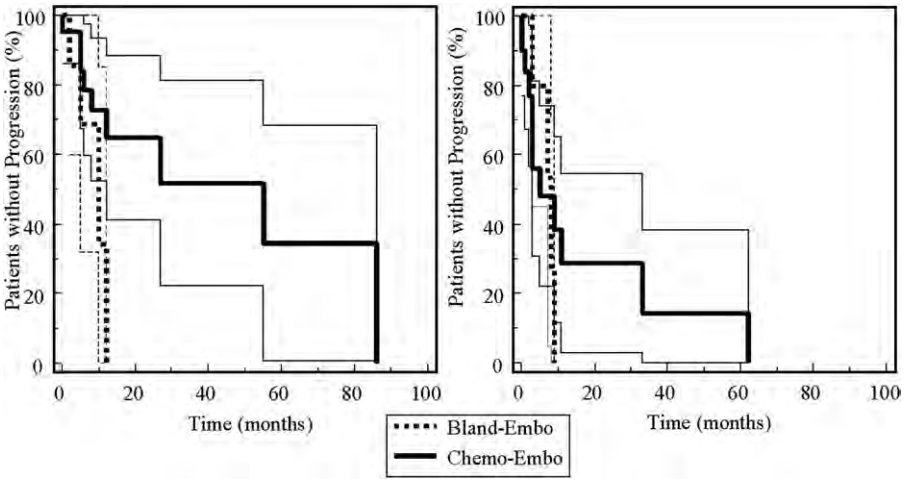

Figure 5. TTP after initial embolization in patients with carcinoid **(a)** and noncarcinoid **(b)** tumors.

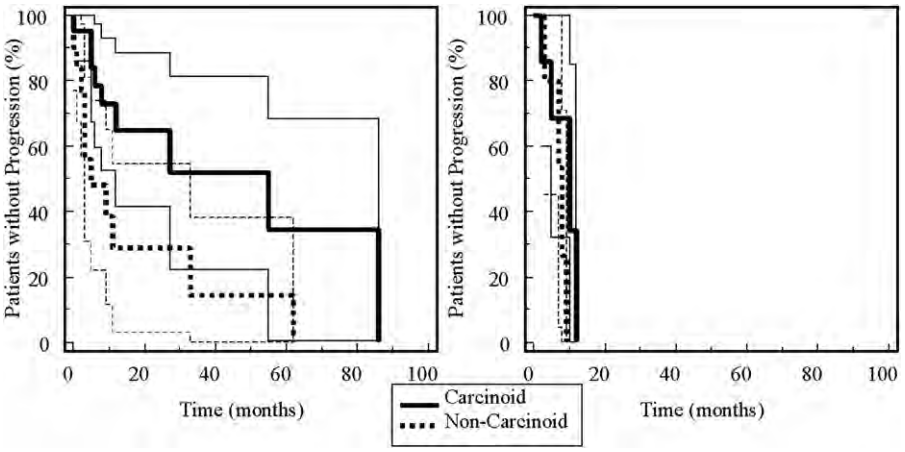

Figure 6. TTP after initial embolization in patients who underwent chemoembolization **(a)** and bland embolization **(b)**.

may be a reflection of the natural history of the disease itself. Indeed, these patients consistently exhibited trends toward improved survival compared with patients without carcinoid tumors when measured from initial diagnosis ($P = .23$; median, 184 months vs 114 months), from the time of detection of liver metastases ($P = .16$; median, 89 months vs 75 months), and from initial embolization ($P = .14$; median, 128 months vs 32 months). No other significant differences were found in patient survival or TTP for any other subgroup of patients, including individuals with hormonally active tumors or those with extrahepatic disease (log-rank test, $P > .05$; **Fig 8**).

DISCUSSION

This retrospective analysis suggests that chemoembolization offers a safe alternative to conventional bland embolization without a significant increase in toxicity. Moreover, chemoembolization may be more efficacious in the treatment of neuroendocrine tumor metastases to the liver—particularly for patients with carcinoid tumors—as measured by initial response and the time to morphologic tumor progression.

Contrary to what may have been expected a priori, chemoembolization and bland embolization have similar associated rates of toxicities. With the exception of infection, the incidence of treatment-related toxicities is not significantly different between these two procedures. Although it should be noted that neither embolic therapy is an entirely benign procedure—some form of postembolization syndrome occurs in most patients—the incidence of severe complications (CTCAE grade ≥3) was fortunately quite low. Even when these did occur, they generally consisted of transient increases of γ-glutamyl transpeptidase or alkaline phosphatase levels or medically controllable pain. More importantly, the length of inpatient hospital stay (a general measure of global clinical toxicity) was identical between patients treated with chemoembolization and bland embolization. Last, a 1.4% mortality rate at 30 days during a total of 219 embolization procedures is in line with the mortality rates associated with other treatment alternatives. These results suggest that chemoembolization is a relatively safe procedure with toxicity similar to that of bland embolization.

Although chemoembolization and bland embolization were associated with similar rates of initial disease stabilization and regression, patients treated with chemoembolization exhibited a longer time to morphologic progression. Although patients with all types of NETs seemed to benefit from chemoembolization, this result was particularly strong for those patients with carcinoid tumors. It may be that some aspect of carcinoid tumor biology lends these cancers to be particularly susceptible to a combination of cytotoxic drugs with a deprivation of blood supply. This result agrees with the previous findings of Moertel et al (6), who demonstrated that carcinoid tumor metastases show increased response (80%) when systemic chemotherapy is combined with ligation or embolization of the hepatic artery than when occlusive therapy is administered alone (60%).

The results of this experiment were also in accordance with the findings of earlier studies of chemoembolization of NET liver metastases. The rate of symptomatic progression, as well as morphologic response, was close to the average observed among other studies (**Table 3**) (8–14,20–22). However, it should be noted that, although most publications regarding chemoembolization of NET metastases re-

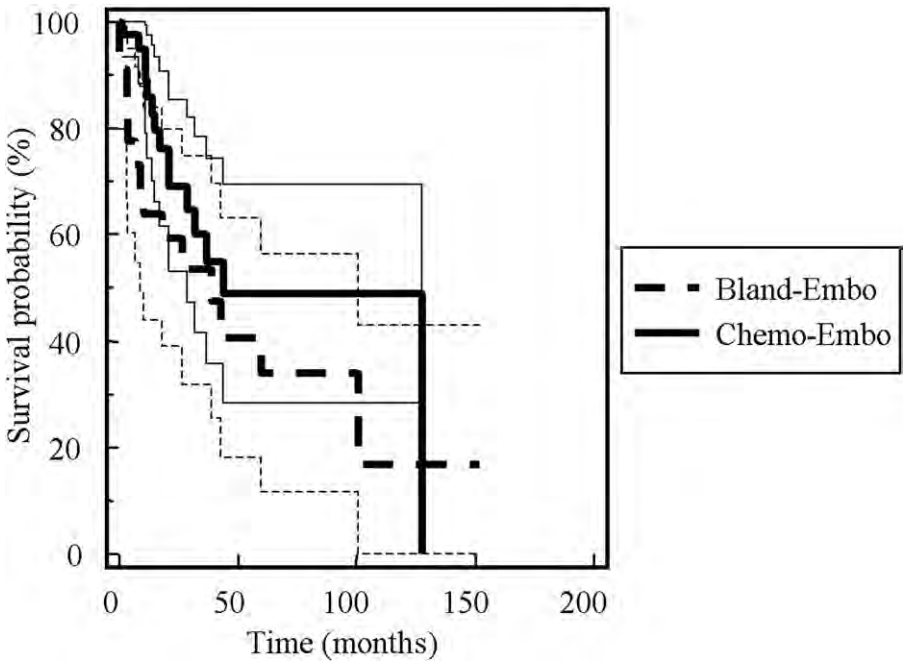

Figure 7. Patient survival after initial embolization.

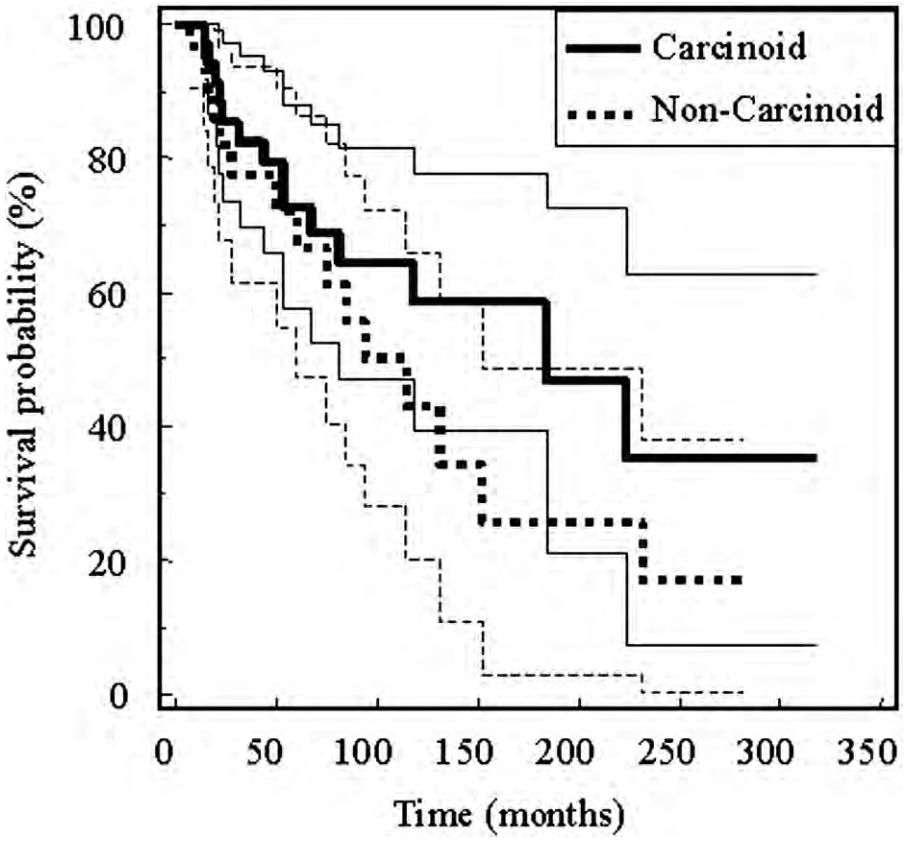

Figure 8. Patient survival from diagnosis.

ported dramatic rates of initial response, there was considerable variation in the reported times to morphologic progression. It remains unclear whether these differences are caused by the considerable intrinsic heterogeneity of neuroendocrine tumors or by differences in treatment among different medical centers.

Despite the dramatic difference between chemoembolization and bland embolization in TTP, a similar difference failed to emerge in TTTF. Although this would seem to imply that bland embolization was ultimately as effective as chemoembolization, it is seems possible that this particular result was caused entirely by a single statistical outlier. As described earlier, one patient who received bland embolization remained responsive to therapy for 85 months, in contrast to the average of 6.3 months among the others.

Last, differences in the TTP of symptoms, as well as ultimate patient survival, demonstrated early trends that seemed to favor chemoembolization. Nevertheless, both these results failed to achieve statistical significance. Perhaps studies with larger sample sizes, lack of crossover, or longer follow-up will be able to resolve this trend.

The conclusions reached by the present study must be approached tentatively. Despite benefiting from a larger sample size ($N = 67$) than previous studies of embolic therapy for NET metastases, there were several sources of bias. First, this study observed the patient populations retrospectively: because individuals were not randomized to the different treatment arms, it is possible that selection bias may have caused disparities between the groups. Although the groups did not differ in pretreatment levels of bilirubin, albumin, or performance status—which are crude measures of disease severity—this criticism cannot be entirely dismissed.

Second, bias could have been introduced into the analysis in the categorization of the patients. For example, some individuals received bland embolization and chemoembolization, and these cases were resolved by assigning the patient into a group based on the predominant therapy administered. Such crossover would be ex-

Table 3
Representative Summary of Chemoembolization Efficacy in Published Studies

Study, Year	No. of Pts.	Tumor Type	Chemboembolization Agents	Adjuvant Therapy	Symptom Response (%)	Time to Symptom Progression (months)	Morphologic Response (%)	Time to Morphoplogic Progression (months)
Hajarizadeh et al (8), 1992	8	Carcinoid	5-FU	Octreotide	100	22	100	10.6
Therasse et al (10), 1993	23	Carcinoid	Doxorubicin	Some on Octreotide	100	—	59	—
Ruszniewski and Malka (18), 1993	24	NET	Doxorubicin	Octreotide	73	—	55	14
Diaco et al (19), 1995	10	Carcinoid	Doxorubicin, cisplatin, mitomycin C	Octreotide, 5-FU	100	—	90	42.5
Mavligit et al (9), 1993	5	Islet cell	Cisplatin, vinblastine	—	—	—	80	18
Clouse et al (20), 1994	20	NET	Doxorubicin	Octreotide	90	—	84	8.5
Perry et al (11), 1994	30	NET	Doxorubicin	Octreotide	90	—	92	—
Drougas et al (12), 1998	15	Carcinoid	5-FU	Octreotide	100	—	93	—
Diamandidou et al (13), 1998	20	NET	Cisplatin	—	67	—	78	—
Current Study	44	NET	Doxorubicin, cisplatin, mitomycin C	Some on Octreotide	92	15	88	27
Average	20				90	19	82	20.1

Table adapted from Kaltsas et al (1).

pected to minimize any differences between chemoembolization and bland embolization outcomes; therefore, the differential effect of chemoembolization could actually be greater than reported.

CONCLUSION

The data from this experiment suggest that chemoembolization of NET metastases to the liver is a relatively safe procedure, with a toxicity profile similar to that of conventional bland embolization. Chemoembolization may be a more efficacious treatment alternative to bland embolic therapy in that it offers a longer time to morphologic progression. This effect is particularly impressive for those patients with carcinoid tumors. It remains unclear whether chemoembolization will ultimately offer a survival benefit for patients because differences between the groups in TTTF and overall survival remained statistically insignificant. Although this study represents the largest retrospective comparison of embolic therapies for the treatment of NET metastases, it lacks the full confidence of a randomized controlled trial. Further investigations are needed to conclusively demonstrate the efficacy of this therapy.

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