Original Article

Chemoembolization of Colorectal Liver Metastases With Cisplatin, Doxorubicin, Mitomycin C, Ethiodol, and Polyvinyl Alcohol

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BACKGROUND: Unresectable colorectal liver metastases have a 1- and 2-year survival of 55% and 33% with current systemic therapies. The authors evaluated response and survival after transarterial chemoembolization. **METHODS:** Chemoembolization with cisplatin, doxorubicin, mitomycin C, ethiodized oil, and polyvinyl alcohol particles was performed at monthly intervals for 1 to 4 sessions. Cross-sectional imaging and clinical and laboratory evaluation were performed before treatment, 1 month after treatment, and then every 3 months. A second cycle was performed for intrahepatic recurrence. Toxicity was assessed using National Cancer Institute's Common Toxicity Criteria version 3.0. Response was evaluated using Response Evaluation Criteria in Solid Tumors criteria. Progression and survival were estimated with Kaplan-Meier analysis. **RESULTS:** A total of 245 treatments were performed over 141 cycles on 121 patients. Ninety-five of 141 treatment cycles were evaluable for response: 2 (2%) partial response, 39 (41%) stable disease, and 54 (57%) progression. Median time to disease progression (TTP) in the treated liver was 5 months, and median TTP anywhere was 3 months. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemoembolization. Survival was significantly better when chemoembolization was performed after first- or second-line systemic therapy (11-12 months) than after third- to fifth-line therapies (6 months) ($P = .03$). Presence of extrahepatic metastases did not adversely affect survival ($P = .48$). **CONCLUSIONS:** Chemoembolization provided local disease control of hepatic metastases after 43% of treatment cycles. Median survival was 27 months overall, and 11 months when initiated for salvage after failure of second-line systemic therapy. ***Cancer*** **2011;117:343–52.** © *2010 American Cancer Society.*

KEYWORDS: colorectal cancer, liver metastases, chemoembolization, liver-directed therapy, survival.

Colorectal carcinoma is the third most common form of cancer in the United States in both men and women, with the second highest mortality. The liver is the most common metastatic site for colon cancer, occurring in 50% to 80% of patients.[1-3] Metastatic disease has a poor prognosis, with a median survival time of approximately 15 to 21 months with regimens of FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and FOLFIRI (folinic acid, fluorouracil, and irinotecan) and 1- and 2-year survival of 55% and 33% with sequential systemic regimens of FOLFOX and FOLFIRI.[4-7] The addition of biologic agents to chemotherapy regimens was demonstrated to improve response rates and time to progression (TTP) over standard chemotherapy in phase 2 and 3 trials. Although an improvement in survival was found in some of studies, median survival remains at 20 to 21 months with the addition of biologic agents.[8-10] Liver-directed therapies such as transarterial chemoembolization offer local effectiveness and the potential for reducing morbidity from hepatic metastases. Several small phase 2 trials have shown promise for chemoembolization,[2,11,12] but a cohort of sufficient size and statistical power to evaluate its impact on survival has not been conducted to date. The purpose of this study is to retrospectively analyze the response rate, survival, and toxicities among patients with colorectal carcinoma liver metastases treated by chemoembolization in our institution.

MATERIALS AND METHODS

Between March 1992 and July 2008, 245 chemoembolizations (mean of 2.0 per patient) were performed over 141 treatment cycles on 121 patients with metastatic colorectal carcinoma. Indication for treatment was most commonly failure of

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systemic chemotherapy to control unresectable liver-dominant disease. Institutional review board approval was obtained for retrospective analysis of this cohort.

Absolute contraindications to chemoembolization included an uncorrectable bleeding disorder, severe thrombocytopenia (platelets <50,000), or leukopenia (white blood cell count <1000/μL), cardiac or renal insufficiency (serum creatinine >2.0 mg/dL), hepatic encephalopathy, jaundice, or dilated intrahepatic bile ducts. Portal vein occlusion was considered a relative contraindication, and chemoembolization was performed only if there were collateral vessels with hepatopedal flow that was demonstrated angiographically. The degree of hepatic compromise was assessed, and the following combination of parameters was considered a contraindication to therapy: lactate dehydrogenase >425 U/L, aspartate aminotransferase >100 U/L, total bilirubin >2.0 mg/dL, and >50% liver volume replaced by tumor.[13]

Within 1 month before treatment, all patients had cross-sectional abdominal imaging (either triple-phase contrast enhanced computed tomography [CT] or contrast enhanced magnetic resonance imaging [MRI]) and thoracic imaging (either plain film or CT), as well as complete blood count, hepatic function panel, coagulation profile, creatinine levels, and carcinoembryonic antigen (CEA) when appropriate.

Informed consent was obtained from all patients. On the day of therapy, a Foley catheter was placed, and vigorous hydration was administered with 200 to 300 mL/h of normal saline until the completion of the procedure, followed by saline at 150 mL/h for a total of 3 L. No diuretics were given. Prophylactic antiemetics (ondansetron 24 mg and dexamethasone 10 mg intravenously) and antibiotics (cefazolin 1 g; metronidazole 500 mg) were administered. Intraprocedural anesthesia was achieved with local 1% lidocaine, intra-arterial lidocaine (200-300 mg/patient), and intravenous midazolam and fentanyl.

In all patients, Seldinger technique was used to access the common femoral artery. Initially, celiac and superior mesenteric angiography was performed, followed by arterial portography via the superior mesenteric artery or splenic artery. The arterial supply to the liver along with any variant anatomy and nontarget arterial supply to the gut were evaluated. The hepatic lobe with the largest tumor burden as determined by preprocedure imaging was treated after superselective catheterization of the appropriate right or left hepatic branch. Microcatheters were used in cases when these arteries could not be selected with a 4 to 5 Fr diagnostic catheter. Chemoembolization material consisted of 10 mg mitomycin C (Mutamycin), 50 mg doxorubicin (Adriamycin), and 100 mg cisplatin (Platinol) dissolved in sterile contrast (8.5 mL) and diluted with 1.5 mL of sterile water. This was emulsified in a 1:1 ratio with ethiodized oil. The emulsification ratio could be adjusted by the operator depending on the size and vascularity of the tumor, with the goal of administering the entire dose of chemotherapy. The emulsification was instilled in 1 to 5 mL aliquots until slowing of flow was achieved. Intra-arterial 1% lidocaine solution was administered in 1 to 3 mL boluses between aliquots of the chemoembolic emulsion. Polyvinyl alcohol particles (0.2 mL of 150-250 μm) were added to the final aliquot, with the goal of achieving near stasis or a tree-in-winter appearance with preservation of antegrade flow in the lobar arteries. The volume of the chemoembolic emulsion administered in any 1 procedure depended on the size and vascularity of the territory treated, and ranged from 3 mL to the maximum of 20 mL. This chemoembolization regimen was used unchanged for the entire cohort. After the procedure, patients received vigorous intravenous hydration (normal saline at 150 mL/h for a total of 3 L), and continued receiving intravenous antiemetics and antibiotics (metronidazole 500 mg every 12 hours, cefazolin 500 mg every 8 hours, odansetron 8 mg every 8 hours, and dexamethasone 8 mg every 8 hours). Pain control was achieved with acetaminophen, codeine, or morphine as required. Patients were discharged from the hospital when oral intake was adequate and when parenteral pain medication was no longer required. An oral antibiotic after discharge was prescribed for 5 days (ciprofloxacin or amoxicillin/clavulanate 500 mg twice daily).

Additional lobar or segmental chemoembolization procedures were performed at monthly intervals until the entire tumor volume was treated. This defined 1 cycle of chemoembolization therapy. Clinical assessment, cross-sectional imaging (either triple-phase contrast enhanced CT or contrast enhanced MRI), and lab data including complete blood count, coagulation profile, hepatic function panel, creatinine, and CEA when appropriate were obtained 1 month after completion of chemoembolization and at 3 month intervals thereafter. If, after initially achieving disease control, there was evidence of intrahepatic tumor progression or recurrence, another cycle of chemoembolization was performed. This was the case in 19 of the 121 patients, for a mean of 1.2 cycles per patient.

Response to each treatment cycle was evaluated using Response Evaluation Criteria in Solid Tumors

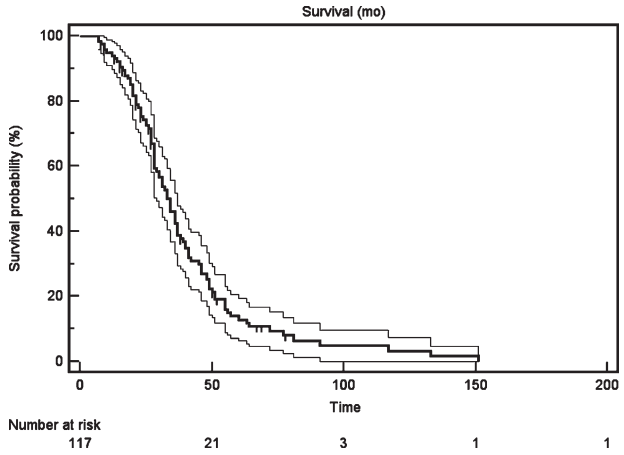

Figure 1. Kaplan-Meier estimate of survival from time of diagnosis of the primary colon cancer is shown, with 95% confidence intervals.

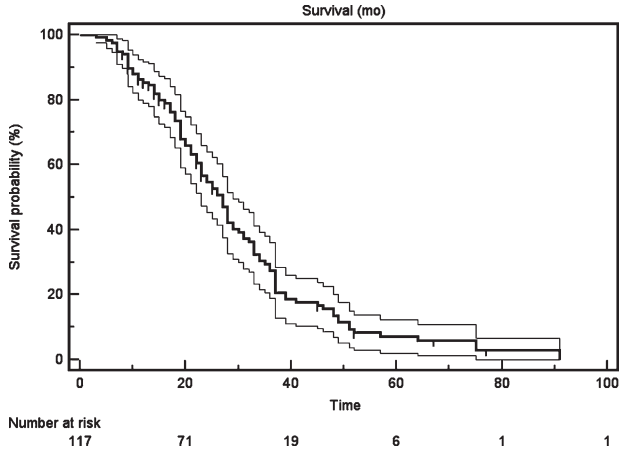

Figure 2. Kaplan-Meier estimate of survival from time of diagnosis of liver metastases is shown, with 95% confidence intervals.

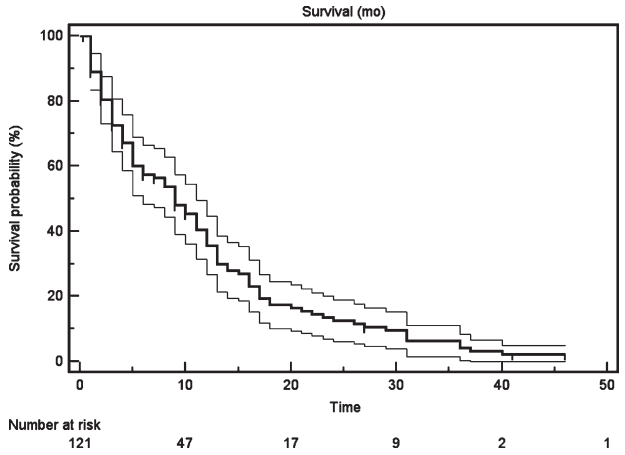

Figure 3. Kaplan-Meier estimate of survival from time of first chemoembolization is shown, with 95% confidence intervals.

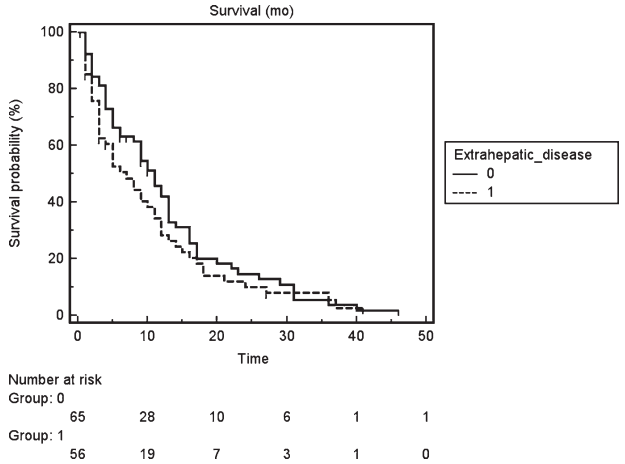

Figure 4. Kaplan-Meier estimates of survival from time of chemoembolization without (solid line) and with (dashed line) extrahepatic disease are shown.

(RECIST) criteria.[14] Partial response was defined as a decrease in the sum of metastases' diameters of at least 30%, progression was defined as an increase of at least 20% or appearance of new metastases, and stabilization was defined as neither of these criteria having been met. When follow-up imaging was not done at our institution, images were obtained whenever possible; otherwise, radiology reports were used to determine response to treatment. Because the RECIST criteria did not yet exist until the latter part of the treatment period, all available imaging was reviewed and retrospectively assessed for response evaluation. When information was available, response to treatment was also assessed using serum levels of CEA. In addition, change in performance status was evaluated using the Eastern Collaborative Oncology Group (ECOG) performance status scale, which was recorded prospectively at the time of each clinical follow-up assessment.

Toxicity was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 on the dimensions of pain, fever, nausea, vomiting, fatigue, weight loss, elevation in serum transaminases, infection, cardiac complications, and any other reported toxicities. In addition, time of in-hospital stay was also recorded after each treatment. Toxicity data were determined retrospectively by reviewing hospital records, discharge notices, nurses' reports, and office visit records.

Survival and TTP results were calculated with Kaplan-Meier curves generated by MedCalc for Windows, version 8.1.0.0 (MedCalc Software, Mariakerke,

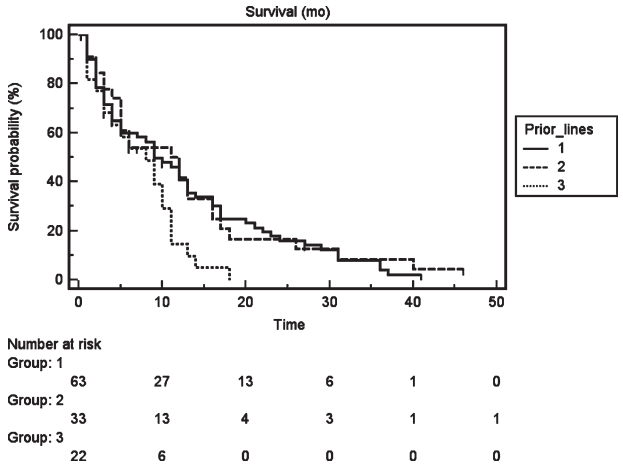

Figure 5. Kaplan-Meier estimates of survival from time of chemoembolization based on number of prior regimens of systemic chemotherapy are shown: 0-1 (solid line), 2 (dashed line), or 3-5 (dotted line).

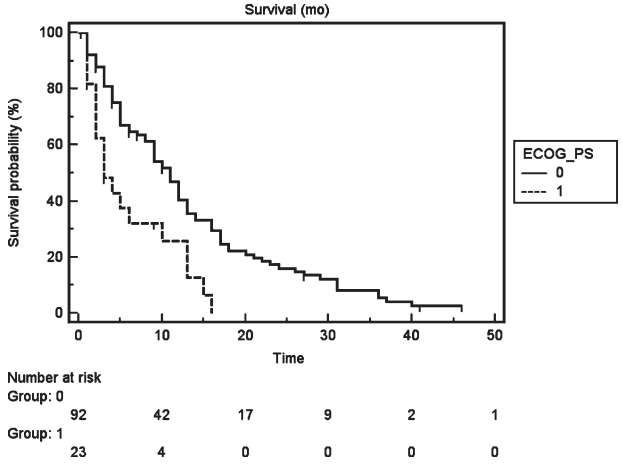

Figure 6. Kaplan-Meier estimates of survival based on Eastern Collaborative Oncology Group performance status (ECOG_PS) are shown: 0 (solid line), >0 (dashed line).

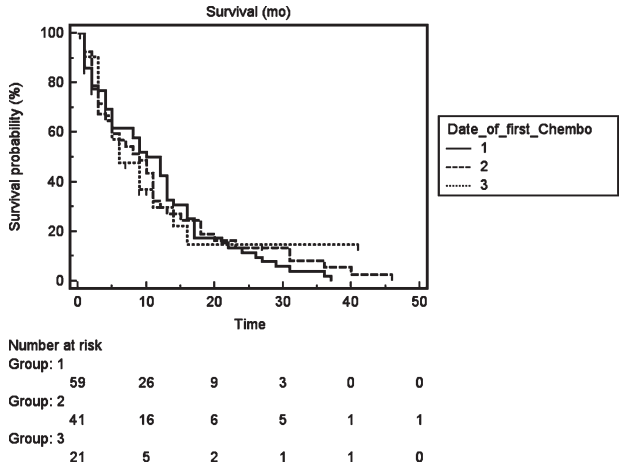

Figure 7. Kaplan-Meier estimates of survival based on era of therapy are shown: before 2000 (solid line), 2000 to 2003 (dashed line), or 2004 to present (dotted line). Chembo indicates chemoembolization.

Table 1. Patient Demographics

Parameter	No. (%)
Men	82 (68)
Women	39 (32)
Mean age, y	61.9
Diagnosis of metastasis	
Synchronous	59 (49)
Metachronous	62 (51)
Extrahepatic metastasis	
Yes	56 (46)
No	65 (54)
Previous lines of chemotherapy	
0-1	63 (52)
2	34 (28)
3-5	22 (18)
Not determined	3 (2)
ECOG performance status	
0	94 (78)
>0	22 (18)
Not determined	6 (4)

ECOG indicates Eastern Collaborative Oncology Group.

Belgium) (Figs. 1-7). Survivorship curves were generated from the time of diagnosis of the primary tumor, from the time of diagnosis of liver metastases, and from time of initial chemoembolization. Subgroup analyses were performed according to number of previous lines of systemic chemotherapy, the presence of extrahepatic disease at the time of first chemoembolization, ECOG performance status at the time of the first chemoembolization, and era of therapy relative to the emergence of new systemic drugs. TTP was calculated in months from the initial treatment in the cycle to the first date of morphologic progression. Recognizing that chemoembolization only treats intrahepatic tumor, progression of disease was calculated for liver-only and for any progression.

RESULTS

Patients had the following characteristics (Table 1): 32% (n = 39) were women, and 68% (n = 82) were men. Average age at the time of diagnosis of the primary colorectal cancer was 62 years. In 49% (n = 59) of patients, the diagnosis of synchronous liver metastases was made at the time of primary diagnosis. For those who did not have

Table 2. Kaplan-Meier Estimates of Survival From Time of Diagnosis of the Primary Colon Cancer, Time of Liver Metastases, and Time of First Chemoembolization, N=121

Survival	Primary Diagnosis	Liver Metastasis Diagnosis	Chemoembolization
Median, mo	33	27	9
1 year	94% (90%-98%)	85% (78%-92%)	36% (27%-45%)
2 year	72% (66%-82%)	54% (46%-64%)	13% (7%-19%)
3 year	40% (33%-51%)	27% (18%-36%)	4% (0-8%)
4 year	23% (17%-33%)	13% (6%-20%)	0
5 year	11% (6%-20%)	5% (0-10%)	0

Standard error at all time points is <5%. Numbers in parentheses are 95% confidence intervals.

synchronous metastatic disease, liver metastases were diagnosed an average of 21 months later. Seventeen percent (n = 20) had previous resection of liver metastases, and 17% (n = 21) received radiofrequency ablation before their first chemoembolization therapy. Forty-six percent (n = 56) of the patients had extrahepatic metastasis at the time of their first chemoembolization treatment. The indication for chemoembolization among patients with extrahepatic disease was a consensus among the medical and interventional oncologists that the liver tumor burden was the dominant risk to the patient. Sites of metastases included lymph nodes, lung, adrenal gland, brain, and bone. Fifty-two percent (n = 63) of the patients had been treated with 0-1 lines of systemic chemotherapy before their first chemoembolization treatment, 28% (n = 34) had received 2 lines of systemic chemotherapy, and 18% (n = 22) had received 3 to 5 prior lines of chemotherapy. Information on previous chemotherapy treatment could not be determined for 3 patients. Performance status was determined for each patient using ECOG performance status criteria. Seventy-eight percent (n = 94) of patients had a performance status of 0 at the time of their first chemoembolization, 18% (n = 22) had a performance status >0, and performance status could not be determined for 6 patients.

A total of 245 chemoembolization procedures (mean of 2.0 per subject) were performed over 141 treatment cycles on 121 patients. Nineteen patients had 2 cycles, and 1 patient had 3. Forty-five patients had no imaging after their last cycle of chemoembolization. Ninety-six treatment cycles, consisting of 174 procedures, were evaluable for response to treatment and TTP. Two (2%) patients had a partial response, 39 (41%) remained stable, and 55 (57%) progressed according to the RECIST criteria. Median TTP of metastases within the treated liver was 5 months. Median TTP of disease anywhere was 3 months.

Response to treatment was also assessed by changes in CEA tumor marker levels. Eighty-four subjects had elevated CEA tumor marker recorded before chemoembolization. Fifty percent (n = 42) experienced a decrease in CEA levels of at least 50% after treatment, among whom 11% (n = 9) patients achieved normal serum levels. In 17% (n = 14), the CEA level decreased <50%, and 27% (n = 23) had an increase in CEA. Five (6%) patients were lost to follow-up.

Dates of death could not be determined for 11 of the 121 patients. These patients were censored from survival analysis at the time of last contact. The exact month of the initial diagnosis of the primary tumor and of appearance of liver metastases was not documented for 4 patients each, who were excluded from the survival analysis for those starting time points. For the entire cohort, including patients with synchronous liver disease at the time of primary diagnosis, median survival was 33 months from diagnosis of the primary tumor, 27 months from development of liver metastases, and 9 months from chemoembolization (Table 2). From primary diagnosis, including patients with synchronous metastases, 1-, 2-, and 5-year survival was 94%, 74%, and 13%, respectively. From time of diagnosis of liver metastases, survival at 1, 2, and 5 years was 85%, 55%, and 6%, respectively. Survival from initial chemoembolization treatment was 36% at 1 year, 13% at 2 years, and 0% at 5 years. For those patients who did not have hepatic metastases at the time of primary diagnosis, median survival was 36 months from primary diagnosis, with 1-, 2-, and 5-year survival rates of 100%, 87%, and 16%.

Subgroup analysis was performed according to the number of previous regimens of systemic chemotherapy at the time of first chemoembolization (Table 3). Survival was significantly better when chemoembolization was performed after first- or second-line systemic therapy than as rescue therapy after failure of 3 to 5 lines of chemotherapy

Table 3. Kaplan-Meier Estimates of Survival From Time of First Chemoembolization

	Prior Systemic Lines			Extrahepatic Disease		Era of Therapy		
Survival	0-1	2	3-5	No	Yes	1992-1999	2000-2003	2004-2010
No.	63	33	22	65	56	59	41	21
Median, mo	12	11	6	11	8	12	9	6
1 year	44%	39%	13%	43%	30%	42%	30%	30%
2 year	18%	13%	0%	13%	12%	11%	13%	13%
HR (95% CI)				0.80 (0.52-1.17)				
P (log-rank)	0.03			0.48		0.99		

HR indicates hazard ratio; CI, confidence interval.
Subgroup analysis is stratified by prior lines of systemic therapies, presence or absence of extrahepatic disease, and era of therapy. Standard error at all time points is <5%. *P* values are derived from log-rank test for difference in survival estimates.

Table 4. CTCAE Toxicity of Chemoembolizations

Grade	Pain	Fever	Nausea	Vomiting	Fatigue	Wt Loss	Bili	ALK	AST	ALT	Inf	Car
1	73%	6%	30%	21%	13%	6%	1%	10%	6%	4%	1%	1%
2	5%	4%	5%	3%	7%	2%	0%	7%	1%	1%	0%	0%
3	4%	2%	1%	1%	3%	0%	1%	2%	1%	1%	0%	0%
4	0%	1%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%
5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Total	82%	13%	36%	25%	24%	8%	1%	19%	7%	6%	1%	1%

CTCAE indicates Common Terminology Criteria for Adverse Events; Wt, weight; Bili, bilirubin; ALK, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Inf, infarction; Car, cardiac complications.
Severity grades 1 to 5 were assigned for each procedure using the CTCAE version 3.0 criteria.

($P = .03$). Survival at 1 and 2 years from time of initial chemoembolization in patients with none or 1 line of systemic chemotherapy was 41% and 16%, respectively; after second-line systemic therapy, 1- and 2-year survival was 42% and 13%, respectively. As rescue therapy after failure of 3 to 5 lines, however, 1- and 2-year survival dropped to 12% and 0%, respectively.

Further subgroup analysis was performed based on the presence of limited extrahepatic disease at the time of first chemoembolization. There was no difference in survival between patients with or without extrahepatic metastases at the time of chemoembolization ($P = .48$). Median survival time for those without extrahepatic disease was 11 months from time of initial chemoembolization, and survival at 1 and 2 years was 43% and 13%, respectively. For those with extrahepatic metastases, median survival was 8 months, and 1- and 2-year survival was 30% and 12%, respectively.

Survival was longer in those with better performance status. Median survival time for those with an ECOG status of 0 at the time of their first chemoembolization was 11 months, as compared with 3 months for those with ECOG status of >0 ($P<.001$; hazard ratio, 0.466; 95% confidence interval, 0.15-0.61).

Finally, survival after chemoembolization was analyzed for 3 eras of therapy: 1) 1990s, before the approval of irinotecan; 2) 2000 to 2003, when irinotecan and oxaliplatin were in use but before the approval of bevacizumab in 2004; and 3) 2004 and onward, when biologic agents were in use. There was no significant difference in survival from time of diagnosis of liver metastases (median 26, 28, and 22 months, respectively, $P = .21$) or from time of first chemoembolization among the 3 eras (Table 2).

Patients spent an average of 1.3 days in the hospital after chemoembolization. Most patients experienced typical symptoms of postembolization syndrome, including pain, fever, nausea, and vomiting. These symptoms were well controlled with pain medication in most patients, usually requiring only 1 night in-hospital stay. Nineteen percent of patients experienced postprocedural toxicities of grade 3 or higher, and 2% of grade 4 or higher (Table 4). Prolonged in-hospital visits after major complications occurred after 11% (n = 20) of the 174 treatments. These complications included extensive hepatic infarction (n = 4), hematoma at the site of catheterization (n = 3), infection (n = 3), acute pulmonary edema (n = 2), myocardial infarction (n = 2), pulmonary embolism (n = 1), transient ischemic attack (n = 1), hypoxia (n = 1), abnormal

heart rhythm (n = 1), voiding difficulty (n = 1), and urethral trauma (n = 1). Thirty-day mortality was 3.6% (4 patients).

DISCUSSION

This retrospective analysis suggests that chemoembolization provides local control of metastatic colorectal carcinoma to the liver during or after standard systemic therapies, and attempts to explore the impact on survival.

The only potentially curative treatment option is surgical resection, which yields a 5-year survival rate of 27% to 55% in recent studies.[15-17] However, resection is available for only a small minority of patients with limited disease. Chemoembolization may be used as second-line therapy after surgical resection to treat recurrent or unresectable liver metastases. This was the case for 17% (n = 20) of the patients in this study who had undergone previous liver resections.

The current standard of care for those who do not qualify for resection is sequential systemic chemotherapy combinations, such as FOLFOX and FOLFIRI, with or without biologic agents such as bevacizumab or cetuximab. Systemic chemotherapy caries a median survival of 15 to 21 months without biologic agents, and 20 to 21 months with the addition of bevacizumab.[4-10] The median survival in this cohort receiving chemoembolization suggests that liver-directed therapy may provide additive benefit.

These results are consistent with prior series. Direct comparison with previous studies is complicated by the heterogeneity of the current literature, in terms of both the chemoembolization protocols used and how outcomes were reported. Nevertheless, the efficacy of chemoembolization has been demonstrated using a variety of chemotherapeutic agents and methods of embolization. Lang and Brown used selective chemoembolization with doxorubicin and ethiodized oil to treat 46 patients with unresectable hepatic metastases.[18] Response to treatment was determined by several criteria, including a decrease in the size and vascularity of the lesions, the presence of necrosis, replacement of the treated lesion with a fibrous scar, and normalization of CEA levels. Complete response to treatment, as determined by the disappearance of the treated lesion and normalization of CEA levels, was achieved in 24% of patients.

In a prospective phase 2 trial by Tellez et al, 30 patients underwent chemoembolization with cisplatin, doxorubicin, and mitomycin C.[3] Bovine collagen material was used for vascular occlusion. An ECOG performance status of 0 to 2 was required to enter the study, and although no specific mention of extrahepatic disease was made, eligibility was limited to those without other active medical illnesses. Response was determined radiographically by a decrease in lesion density in at least 75% of the lesion or a decrease in size by at least 25% on CT. Alternatively, biological response was considered a decrease in CEA levels of at least 25% from baseline. Radiologic response was achieved by 63%, biological response by 95%, and either response by 82% of patients. A phase 2 trial by Sanz-Altamira et al performed chemoembolization on 40 patients with 5-fluorouracil (1000 mg), mitomycin C (10 mg), and ethiodized oil (10 mL).[11] Vascular occlusion was achieved with gelatin sponge embolization. Exclusion criteria were similar to those in Tellez et al[3] and our study, except for the explicit exclusion of any patient with extrahepatic disease likely to be life-threatening within 3 months. Response to treatment was determined by lesion diameter as measures on CT, with a partial response defined as a >50% reduction in the diameters of the indicator lesions. The authors found a 22.8% partial response rate by these criteria.

Given the heterogeneity of response assessment among prior studies, survival data may provide a more standardized means of comparison. Median survival in the Tellez et al[3] trial was 29 months from diagnosis of metastases and 8.6 months from the time of first chemoembolization. When considering these results, it should be noted that chemoembolization treatments were performed at an interval of 6 to 8 weeks, as opposed to the 4-week interval used in our study. In the Sanz-Altamira et al[11] trial, the authors found a median survival of 10 months from first chemoembolization. Survival results in both of these trials are consistent with those found in our study.

Larger studies have also demonstrated efficacy of chemoembolization for treatment of metastatic colorectal cancer. A recent prospective study by Vogl et al included 463 patients who received chemoembolization with mitomycin C alone (52.5%), mitomycin C and gemcitabine (33.0%), or mitomycin C and irinotecan (14.5%), depending on previous chemotherapy treatments, followed by Lipiodol and starch microspheres for embolization.[19] Exclusion criteria were similar to those used in our study, with 2 major exceptions. First, those patients with extrahepatic metastases were excluded. Also excluded were those with a poor Karnofsky score (<70). This roughly limited the patient population to those with an ECOG

performance status of 0, for easier comparison to the results of our study. By using RECIST criteria, the authors found a partial response rate of 14.7%, stable disease in 48.2%, and progressive disease in 37.1%. This represents greater disease control than that found in our study (63% vs 43%). They reported a median survival of 38 months from diagnosis of liver metastases, and 14 months from the start of chemoembolization, with no statistically significant difference in the survival between groups with different chemotherapeutic drug combinations. These survival times are longer than those found in our study. Some of the discrepancy may be attributed to the characteristics of the patient population, such as exclusion of patients with poor performance status.

Assessment of morphologic response and TTP is problematic for liver-directed therapies such as chemoembolization, because the entire tumor burden is not treated at the same time. For patients requiring 2 to 3 monthly lobar or segmental embolizations, there is a substantial time difference between treatment of the first and last metastases. This results in multiple confounding factors; the tumors treated last had more time to progress between the baseline imaging and therapy, and less time to show a response, whereas those embolized first had less time to progress and more time to respond. The relatively lower response rate and short TTP in this cohort may reflect these artifacts in assessment caused by imaging only after completion of the entire cycle of chemoembolizations. TTP analysis may be confounded by use of other therapies. Because liver-directed therapy is only a component of the multidisciplinary care of the patient with metastatic colon cancer and is often intercalated with systemic therapies, overall survival is the more relevant clinical outcome.

The question of survival benefit would be more clearly addressed in a randomized trial. Such a trial was attempted from 1997 to 2003 by the National Cancer Institute through the American College of Radiology Imaging Network (ACRIN protocol 6655) and ECOG, in which patients initiated systemic therapy and were then randomized to also receive chemoembolization in the experimental arm or systemic therapy only in the control arm. The rapid evolution of systemic chemotherapy for colon cancer during this time period as new drugs were approved resulted in repeated redesign of the trial to avoid obsolescence in the control arm, and the trial was abandoned when a consensus was reached that systemic therapy regimens for this disease were too unstable to serve as a control for a 4- to 5-year survival study.

The findings in the subgroup analyses may provide important information regarding the indications for chemoembolization. The presence of significant extrahepatic disease has been considered a relative contraindication for liver-directed therapy such as chemoembolization,[20] and several prior studies excluded those with extrahepatic disease.[19,21,22] The finding that survival in our series was similar in those patients with and without limited extrahepatic disease at the time of initial chemoembolization supports the concept that the liver metastases are responsible for most mortality among patients with limited extrahepatic disease, and suggests that the presence of limited extrahepatic disease should not be a contraindication to liver-directed therapy. However, as this was a retrospective study, selection bias may have influenced these findings. Specifically, those patients treated with chemoembolization may have had minimal extrahepatic disease as compared with the spectrum of all patients who present with stage IV disease. It should be noted that our findings are inconsistent with the earlier report of Sanz-Altamira et al, who found that patients with disease confined to the liver had a significant survival advantage over those with extrahepatic disease (median 14 months vs 3 months, $P < .02$).[11]

Survival rates were significantly better for those patients who received chemoembolization after 0, 1, or 2 lines of systemic chemotherapy than for those who received chemoembolization as salvage therapy after 3 to 5 lines of systemic therapy. Of particular interest is the observation that survival when chemoembolization was performed after failure of the standard 2 lines of systemic therapy was just as good as when performed earlier in the patient's course. The median survival of 11 to 12 months when chemoembolization was used as third-line therapy is better than would be expected from salvage systemic regimens. This may suggest a role for chemoembolization earlier in the course of treatment, either integrated with standard systemic first- or second-line regimens or immediately after their failure, as opposed to only after the failure of another salvage systemic regimen. It should be noted that earlier work by Sanz-Altamira et al found that prior therapy was not associated with any survival advantage.[11] It is unclear, however, how prior treatment was analyzed.

Analysis based on era of therapy indicated that there was no significant survival advantage for those treated since the introduction of bevacizumab over those who received treatment in earlier therapy eras. The results of addition of bevacizumab to liver-directed therapy is of

particular interest because of the potential synergistic effect between chemoembolization and bevacizumab. The ischemic necrosis provided by chemoembolization may be bolstered by slower revascularization because of the anti-angiogenic effects of bevacizumab. Conversely, extensive pretreatment with bevacizumab diminishes tumor blood flow and may limit intra-arterial delivery of chemotherapeutic agents. Recent trials indicate that the addition of the biologic therapy to systemic chemotherapeutic regimens improves response rates among those with metastatic colorectal cancer.[8-10] A pilot study comparing chemoembolization alone to chemoembolization with bevacizumab in hepatocellular carcinoma (HCC) patients with unresectable disease has demonstrated prolonged disease control with combination therapy, and a phase 2 trial is currently underway to examine the relationship between these modalities.[23,24] If the preliminary findings hold up in larger HCC trials, the same logic may be applied to the treatment of other hepatic lesions, including colorectal metastases. It should be noted, however, that although improved response rates with bevacizumab have been demonstrated, a clear survival benefit has not been established as consistently. A phase 3 trial by Saltz et al failed to show a significant improvement in overall median survival with the addiction of bevacizumab to oxaliplatin-based chemotherapy regimens despite significant improvements in progression-free survival.[10]

Liver-directed therapy with yttrium 90 microsphere radioembolization is another option for unresectable hepatic metastases. A recent study by Sato et al described a median survival time of 15.2 months from the first radioembolization treatment, with 1- and 2-year survival rates of 53.7% and 26.7%, respectively.[25] Common toxicities from radioembolization were similar to the postembolization syndrome after chemoembolization, including fatigue, pain, and nausea.

A recent innovation is chemoembolization using drug-eluting microspheres loaded with irinotecan as opposed to conventional oily emulsion. High and sustained intratumoral drug levels with very low systemic exposures are achieved with this alternative platform. Early single-center and registry reports suggest a brisk early response rate, particularly those using tumor enhancement criteria, but even conventional RECIST responses are impressive compared with those reported for oily chemoembolization.[26,27] Acute toxicity has been reported to be more severe and require specific measures for mitigation.[28] Impact on progression-free and overall survival is still in the immature phase of analysis, but results are sufficiently encouraging that the drug-eluting bead platform has been incorporated into several first-line and second-line phase 2 and randomized trials worldwide.

Toxicities found in this study are consistent with those expected from previous work. The majority of patients experienced a typical postembolization syndrome including pain, fever, nausea, and vomiting.[29] These symptoms were well controlled with medication. Similar postembolization symptoms were common findings in other previous studies as well.[3,11,12] A severe complication rate of 8% is close to that found in earlier studies. In addition to the severe complications mentioned above in this study, complications in other studies included gallbladder necrosis, contrast-induced acute renal failure, and liver abscess.[3,11,21]

The design of this study lends itself to several biases. The study was retrospective, which allows for the possibility for selection bias. Implicitly, only those patients thought to be able to benefit from chemoembolization received the treatment. Many patients received standard systemic therapy in the community and were only referred once therapy had failed, yet they still maintained adequate performance status and liver-dominant disease to qualify for liver-directed therapy; patients with a more aggressive cancer would have already died and not be referred into this cohort. Because the study was done at a tertiary care center with a broad geographic referral base, many patients received follow-up assessment and subsequent therapies at outside institutions, and did not return after completion of their liver-directed therapy. Therefore, inconsistencies may have been present in the assessment of clinical progression.

Conclusions

Our limited experience suggests that chemoembolization is effective in achieving disease stabilization for hepatic metastasis from colorectal carcinoma, providing local disease control after 43% of treatments. The median survival of 33 months from initial diagnosis, 27 months from the time of liver metastasis, and 9 months from the start of chemoembolization suggests a possible improvement over reported survival times for systemic therapies alone. A significant survival advantage was found for those receiving chemoembolization earlier in their course of treatment over those who received it after failure of salvage systemic regimens. The presence of limited extrahepatic disease did not adversely impact survival after liver-directed therapy. An additional survival advantage was observed in those

who were treated in the era of biologic therapy with bevacizumab. Further investigation into chemoembolization treatment is merited to determine its palliative and therapeutic potential in conjunction with systemic treatments, if a sufficiently stable control arm can be defined or a dealer's choice strategy used to allow for evolution in systemic therapy.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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