# Repeated Transarterial Chemoembolization in the Treatment of Liver Metastases of Colorectal Cancer: Prospective Study

**Purpose:** To evaluate local tumor control and survival data after transarterial chemoembolization with different drug combinations in the palliative treatment of liver metastases in patients with colorectal cancer.

**Materials and Methods:** The study was approved by institutional review board, and informed consent was obtained from all patients included in the study. A total of 463 patients (mean age, 62.5 years; range, 34.7–88.1 years) with unresectable liver metastases of colorectal cancer that did not respond to systemic chemotherapy were repeatedly treated with chemoembolization in 4-week intervals. In total, 2441 chemoembolization procedures were performed (mean, 5.3 sessions per patient). Of 463 patients, 67.4% had multiple (five or more) metastases, 8% had one metastasis, 10.4% had two metastases, and 14.3% had three or four metastases. The local chemotherapy protocol consisted of mitomycin C alone \( n = 243 \), mitomycin C with gemcitabine \( n = 153 \), or mitomycin C with irinotecan \( n = 67 \). Embolization was performed with lipiodol and starch microspheres for vessel occlusion. Tumor response was evaluated with magnetic resonance imaging. The change in tumor size was calculated and the response was evaluated according to the Response Evaluation Criteria in Solid Tumors. Survival rates from first diagnosis and from first chemoembolization session were calculated according to the Kaplan-Meier method. Follow-up imaging was performed until patient death.

**Results:** Evaluation of local tumor control resulted in partial response (68 patients [14.7%]), stable disease (223 patients [48.2%]), and progressive disease (172 patients [37.1%]). The 1-year survival rate after chemoembolization was 62%, and the 2-year survival rate was 28%. Median survival from date of diagnosis of liver metastases was 38 months and from the start of chemoembolization treatment was 14 months. There was no statistically significant difference between the three treatment protocols.

**Conclusion:** Chemoembolization is a minimally invasive therapy option for palliative treatment of liver metastases in patients with colorectal cancer, with similar results among three chemoembolization protocols.

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1 From the Department of Diagnostic and Interventional Radiology, University Hospital Frankfurt, Johann Wolfgang Goethe-University, Theodor-Stern Kai 7, D-60590 Frankfurt am Main, Germany. From the 2006 RSNA Annual Meeting. Received February 13, 2008; revision requested April 10; revision received June 3; accepted July 1; final version accepted July 22. Address correspondence to T.J.V. (e-mail: T.Vogl@em.uni-Frankfurt.de). © RSNA, 2009
Liver metastases of colorectal cancer are a major challenge and a substantial problem in clinical oncology. For colorectal cancer, the liver is the most common site of manifestation and liver metastases are the leading cause of death (1). Liver metastases are present in 60%–70% of patients with colorectal cancer and in 20%–50% of patients at the time of initial diagnosis (2–4). Currently, the only curative treatment in patients with liver metastases of colorectal cancer is liver resection (5,6). In addition to systemic chemotherapy, current therapies of unresectable liver lesions include hepatic arterial infusion of chemotherapeutic drugs, transarterial chemoembolization, radiofrequency ablation, cryotherapy, laser-induced thermotherapy (LITT), and yttrium-90 radioembolization (7–10).

Chemoembolization is defined as a selective administration of chemotherapy usually combined with embolization of the vascular supply to the tumor. This treatment results in selective ischemic and chemotherapeutic effects on liver metastases (11). Chemoembolization is based on the concept that the blood supply to hepatic tumors originates predominantly from the hepatic artery (12,13). Therefore, embolization of the hepatic artery can lead to selective necrosis of the liver tumor while it leaves normal parenchyma virtually unaffected (13,14). It has been shown that anoxic damage increases vascular permeability and thereby promotes penetration of chemotherapeutic agents into the tumor (13,15). However, number, location, and size of the tumors, status of tumor capsule, blood supply to the cancer, and the interventional skill of the angiographer might influence the response to chemoembolization treatment (13,16,17).

The current study was performed in a large number of patients to determine the tumor response and survival rates among patients with liver metastases of colorectal cancer undergoing chemoembolization and to compare the effect of three different chemoembolization regimens.

**Materials and Methods**

Between February 1999 and July 2006, 463 patients (167 women, 296 men) with liver metastases of colorectal cancer underwent repeated transarterial chemoembolization. At the time of initial chemoembolization, the mean age of the patients was 62.5 years (age range, 34.7–88.1 years). The primary tumor was located in the rectum in 145 patients and in the colon in 318 patients. The prospective study was approved by the institutional review board. Informed consent was obtained for all patients.

The indications for chemoembolization were unresectable liver metastases showing no response, disease progression, or toxicity to systemic chemotherapy. The tumor load of the liver was restricted to less than 70% of the total liver volume. The presence of extrahepatic metastases was excluded by means of abdominal and chest computed tomographic (CT) scanning.

Before each treatment, specific laboratory values were monitored. These included a complete blood cell count, blood platelet count, hemoglobin level, bilirubin level, creatinine level, alanine aminotransferase and aspartate aminotransferase levels, cholesterol level, and coagulation values to ensure that the patient did not have any contraindication to chemoembolization treatment.

Contraindications to treatment with chemoembolization were poor performance status (Karnofsky 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, and cardiovascular and respiratory failure were also exclusion criteria. To ensure adequate treatment compliance, patients had to be in a good mental state and had to be able to provide their own consent. All patients were treated on an outpatient basis.

**Implication for Patient Care**

- **Chemoembolization is an effective therapy for neoadjuvant, symptomatic, or palliative treatment of liver metastases in patients with colorectal cancer; despite the three different chemoembolization protocols used, results were similar among the groups.**
arteries. For superselective embolization, an infusion catheter was used.

For patients with bilobar disease, the treatment was performed to control the lobe with the higher tumor burden as seen at magnetic resonance (MR) imaging performed immediately before the procedure; the second lobe was handled in another session.

The chemotherapeutic suspension consisted of mitomycin C alone (8 mg/m²), mitomycin C with gemcitabine (Gemzar, Lilly Pharma, Giessen, Germany; 1000 mg/m²), or mitomycin C with irinotecan (Campto, Pfizer Pharma, Karlsruhe, Germany; 150 mg/m²). The embolization was performed (after drug injection) with a maximum of 15 mL/m² iodized oil (lipiodol), followed by an injection of 200–450 mg of starch microspheres (200 µm) (EmboCept; PharmaCept, Berlin, Germany) for vessel occlusion.

The inclusion criteria for chemotherapeutic agents were as follows: All patients had been treated with at least one treatment protocol of second-line standard for metastatic colorectal cancer therapy. None of the patients included in the current study underwent LITT or radiofrequency ablation before the start of chemoembolization treatment. All patients who had undergone both oxaliplatin- and irinotecan-containing protocols (FOLFOX and FOLFIRI, respectively) were treated with only mitomycin (n = 243). Patients who had undergone a previous irinotecan-based protocol were treated with a combination of mitomycin and gemcitabine (n = 153), and patients who had undergone oxaliplatin-based second-line treatment were treated with a combination of mitomycin and irinotecan (n = 67).

The embolization suspension was injected slowly with fluoroscopic control until stasis of the blood flow was observed. After embolization, devascularization was confirmed with additional angiography of the hepatic artery. This study was designed to include the performance of at least three sessions of repeated chemoembolization, with treatment intervals 4 weeks apart. The end point for chemoembolization treatment was defined as a state of stable disease for two successive sessions or as disease progression.

The morphologic tumor response (number, localization, and size) was evaluated with MR imaging. For initial treatment planning, unenhanced and contrast material–enhanced MR imaging with 0.1 mmol of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) per kilogram of body weight was performed in all patients. A conventional 1.5-T system (Magnetom Symphony; Siemens, Erlangen, Germany) was used.

The MR imaging protocol included T1-weighted unenhanced and contrast-enhanced two-dimensional fast low-angle shot gradient-echo sequences with transverse and sagittal section orientation (repetition time msec/echo time msec, 135/6; flip angle, 80°; field of view, 350 mm; matrix, 134 × 256; section thickness, 8 mm). In addition, unenhanced T2-weighted turbo spin-echo sequences (3800/92; flip angle, 150°; field of view, 350 mm; matrix, 155 × 256; section thickness, 8 mm) and dynamic volume-interpolated breath-hold sequences (4.5/1.8; flip angle, 15°; field of view, 350 mm; matrix, 128 × 256; section thickness, 8 mm) were used for the differentiation of the lesions after administration of a contrast medium.

Unenhanced MR imaging was performed with one of two systems after every chemoembolization cycle. A conventional 1.5-T system, as described previously, was used to perform two-dimensional fast low-angle shot sequences in transverse and sagittal section orientation (135/6; flip angle, 80°; field of view, 350 mm; matrix, 134 × 256; section thickness, 8 mm) and T2-weighted turbo spin-echo sequences (3800/92; flip angle, 150°; field of view, 350 mm; matrix, 155 × 256; section thickness, 8 mm). A 0.5-T system (Privileg; Elscint, Haifa, Israel) was used to perform gradient-echo sequences (450/14; flip angle, 180°; field of view, 350 mm; matrix, 180 × 256; section thickness, 8 mm).

Twenty-four hours after embolization, retention of iodized oil in the tumor and the liver parenchyma was verified with findings at unenhanced CT in consensus. CT was performed with the spiral technique (section thickness, 8 mm) by using a four-section CT scanner (Somatom Plus 4, Siemens).

Follow-up imaging after treatment was performed every month during the first 3 months and then every 3 months thereafter until patient death. None of the patients included in the current study were lost to follow-up. In case of progression after initial stabilization or regression, chemoembolization was repeated by using the same protocol previously described, as long as the patient still met the inclusion criteria for chemoembolization.

Quantitative and Statistical Evaluation
Clinical and radiologic data in all patients with liver metastases of colorectal cancer undergoing chemoembolization were prospectively evaluated. All clinical data were obtained by contacting patients and relevant doctors, reviewing the database of chemoembolization and patient files, and analyzing MR imaging and CT studies. All MR imaging and CT evaluations were performed by two radiologists (with more than 5 [J.O.B.] and 15 [T.J.V.] years of experience in abdominal imaging) in consensus. Data were entered as events occurred.

All responses are based on findings at MR imaging. Measurement of the target metastases was performed by using transverse imaging to evaluate the longest cross-sectional diameter as the length and the associated perpendicular diameter as the width. The longest diameter was also measured on sagittal images to acquire a third measurement in order to obtain the longest dimension of the lesion.

The change in size was calculated by means of MR imaging and the response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria based on the longest dimension (19).

Complete response was defined as the total disappearance of all known lesions. Partial response was defined as a reduction of 30% or more of the target lesions and no new lesions. Stable dis-
ease was defined as reduction of less than 30% or an increase of less than 20% in the target lesions with no significant newly developing lesions. Stable disease was present when it met neither partial response nor progressive disease criteria. Progressive disease was defined as the growth of new lesions and/or increase of target lesion size of at least 20% in longest dimension.

Statistical analysis was performed by using BiAs 8.3.6 software (Epsilon, Darmstadt, Germany). Survival times from the first chemoembolization procedure and from the date of diagnosis of liver metastases were calculated to obtain the median survival times by using the Kaplan-Meier method (20).

The indication for chemoembolization of liver metastases in patients with colorectal cancer was primarily palliative. During the course of treatment, the indication for treatment changed to symptomatic or even neoadjuvant in some patients.

Neoadjuvant chemoembolization was defined as a clinical scenario where chemoembolization resulted in a relevant downsizing in size and number of metastases so that local thermal ablation with LITT could be performed. The criteria for LITT were defined as five or fewer metastases and a size of 5 cm or smaller in diameter. Patients who met such inclusion criteria for LITT treatment before chemoembolization also underwent chemoembolization before LITT to decrease the tumor activity and tumor vascularity and thus maximize the ablative effect of LITT on the tumor.

Palliative chemoembolization was defined as therapy for asymptomatic patients intended mainly to prolong survival and to preserve and improve the quality of life without curing the disease. Symptomatic treatment was defined as a therapy intended to alleviate or decrease tumor-related symptoms (eg, pain, bulk related symptoms).

Patient Population

The results in 463 patients (167 women, 296 men) with colorectal unresectable liver metastases that had not responded to systemic chemotherapy were analyzed. For patients included in the current study, systemic chemotherapy treatment of liver metastases was stopped, and the patients received only chemoembolization sessions as a local treatment for liver metastases. In total, 2441 chemoembolization sessions were performed in 4-week intervals, with a mean of 5.3 (range, 3–24) sessions per patient.

Results

MR Findings

The morphologic response of hepatic lesions was verified at MR imaging. The number of liver metastases as was follows: 8% (37 of 463) of all patients had one metastasis, 10.4% (48 of 463) had two metastases, 14.3% (66 of 463) had three or four metastases, and 67.4% (312 of 463) had multiple (five or more) liver metastases of colorectal cancer. Chemoembolization treatments were performed with mitomycin C alone (243 patients), mitomycin C and gemcitabine (153 patients), or mitomycin C and irinotecan (67 patients).

The evaluation after chemoembolization revealed a partial response in 14.7% (68 of 463) of patients (Fig 1), progressive disease in 37.1% (172 of 463) (Fig 2), and stable disease in 48.2% (223 of 463) (Fig 3) according to the RECIST criteria. The maximum response was observed 12 weeks after the first chemoembolization.

In the group that received mitomycin C only, we observed partial response in 13.6% (33 of 243) of patients, stable disease in 49.4% (120 of 243), and progressive disease in 37% (90 of 243). In the group that received mitomycin C and irinotecan, we observed partial response in 19.4% (13 of 67) of patients, stable disease in 44.8% (30 of 67), and progressive disease in 35.8% (24 of 67). In the group that received mitomycin C and gemcitabine, we observed partial response in 11.1% (17 of 153) of patients, stable disease in 53.6% (82 of 153), and progressive disease in 35.3% (54 of 153). During therapy the clinical situation changed: 335 patients (72.4%) were treated palliatively, 68 patients (14.7%) were treated symptomatically, and 60 patients (12.9%) were treated neoadjuvantly.

In 60 patients (12.9% of all patients included in the current study) in the partial response group, there was a relevant downsizing in size and number of metastases at presentation, which made the candidates eligible for a percutaneous ablative procedure such as LITT. This group of patients included candidates from the mitomycin C–only group (n = 33), the mitomycin C and irinotecan group (n = 10), and the mitomycin C and gemcitabine group (n = 17).

Survival Analysis

Survival analysis was performed by using the Kaplan-Meier method. Median survival time from primary diagnosis of liver metastases of colorectal cancer was 38 months, and median survival time from the start of chemoembolization was 14 months. Results of treatment from initial diagnosis of liver metastases (Fig 4) indicated that the 1-year survival rate was 96%, 2-year survival was 80%, and 3-year survival was 56%; the 1-year survival rate after the first chemoembolization was 62%; however, the 2-year survival rate was reduced to 28%.

Median survival of patients after chemoembolization therapy with mitomycin C (Fig 5) or a combination of mitomycin C and irinotecan was 14 months, and median survival of patients after chemoembolization treatment with a chemotherapeutic combination of mitomycin C and gemcitabine was 13.9 months. For survival times from the start of chemoembolization, no statistically significant difference was found between the three groups by using the log-rank test (Peto-Pike χ² value, 1.2556; P = .534).

Median survival time of patients was 17.6 months with neoadjuvant treatment, 14 months with palliative treatment, and 8 months with symptomatic treatment. The study showed 78%, 35%, and 12% survival rates among patients with neoadjuvant treatment at 1, 2, and 3 years, respectively (Fig 6). The 1-year survival rate of patients with palliative treatment was 64%; the 2-year survival rate was reduced to 28%. The 1-year survival rate of patients with symptomatic therapy was
34%, and 2-year survival rate had been reduced to 13%. Log-rank test Peto-Pike $\chi^2$ value was 24.7161 ($P < .001$). The calculated value indicates a statistically significant difference.

Extrahepatic metastases developing and/or recurring in the course of disease in almost the same manner as intrahepatic metastases are the main unsolved problem. After the first chemoembolization cycle, 75 patients had extrahepatic metastases (such as lung, brain, bone, spleen, and peritoneum) that had previously responded to systemic chemotherapy. Patients with developing extrahepatic metastases had a median survival of 12 months.

The median survival of patients with partial response was 18.2 months (Fig 7), that of patients with stable disease was 13.5 months, and that of patients with progressive disease was 13 months. With the log-rank test, Peto-Pike $\chi^2$ value was 8.3969 ($P = .015$); the calculated value indicates a statistically significant difference.

Combined chemoembolization and MR imaging–guided LITT has been used in the treatment of unresectable hepatic metastases. Thus, patients with morphologic reduction of liver lesions after chemoembolization are candidates for LITT. In the study, 60 patients were treated with LITT 4–6 weeks after final chemoembolization.

Patients were monitored for potential complications and “postembolization syndrome.” Generally, the majority of patients tolerated chemoembolization well, and all patients were discharged on the day of treatment. However, a small group of patients had symptoms of abdominal pain, nausea, and vomiting for 2–7 days.

Discussion

Metastases are the most common malignant tumors of the liver. Most metas-
tases of the liver originate from primary malignancies of the gastrointestinal tract and breast cancer because the liver has a filter function of the portal blood stream (21). Surgical resection results in a median survival of 28–46 months, and 5-year survival rates range from 24% to 40% (22). For patients without surgically resectable liver metastases, chemoembolization through the hepatic artery has been an effective treatment.

Vessel occlusion agents such as iodized oil (lipiodol) and starch microspheres have shown promising results. These suspensions occlude small tumor vessels and cause obstruction in the vascular bed of liver tumors. This approach to therapy is known to reduce systemic toxicity and increase local toxicity (23,24).

Lipiodol and starch microspheres concentrate and prolong the retention of the chemotherapeutic agent in the tumor (25). This effect can be used in treatment of colorectal liver metastases with chemoembolization. Chemoembolization as a treatment possibility has been shown in numerous studies. As a combination of local arterial application of cytostatic drugs, chemoembolization is an effective and recommended therapy of colorectal metastases of the liver (26). Effectiveness and results of chemoembolization, responses, and survival have formed the basis for several reports.

Our results showed that median survival time for patients with colorectal liver metastases was 38 months from the primary diagnosis of liver metastases and 14 months from the beginning of chemoembolization therapy. These results are in comparison to 7–8 months survival for untreated patients (13).

In the prospective nonrandomized study of Sanz-Altamira et al (27), 40 patients (median age, 60 years) underwent chemoembolization with 1 mg of 5-fluorouracil, 10 mg of mitomycin C, and 10 mL of iodized oil followed by gelfoam. All patients had bidimensionally measurable disease at CT, ultrasonography, or MR imaging.

Figure 2: Progressive disease after 9 months of chemoembolization in 52-year-old patient with unresectable liver metastases of colorectal cancer (T3N2M1) showing no response during systemic chemotherapy. (a) Pretreatment unenhanced transverse T1-weighted MR image shows lesions in segments IV, V, and VI. (b) CT scan after selective transarterial embolization shows bilobar lesions with a metastasis showing a high degree of retention of iodized oil (lipiodol) in segment VII and a lower degree of lipiodol retention in segment II. (c) Posttreatment unenhanced transverse T1-weighted MR image after 10 sessions of chemoembolization shows progression of all liver lesions, especially in segment IV.
In 22.8% of patients there was a partial response. These results are comparable with our study results observed in the mitomycin–irinotecan group. However, these results were still higher than what was observed in the mitomycin only or the mitomycin–gemcitabine group. In the study by Sanz-Altamira et al (27), the median duration of response was 7 months. The patients had a median survival of 10 months after start of chemoembolization. In a study by Wasser et al (28), 21 patients (mean age, 62 years) underwent chemoembolization with mitomycin C and degradable starch microspheres. In that study, the authors retrospectively investigated survival, response, and side effects after chemoembolization. Follow-up was performed by using contrast-enhanced spiral CT. The median survival was 13.8 months. The results of Wasser et al almost coincide with our study results, in which median survival was 14 months for the mitomycin only and mitomycin plus irinotecan groups and 13.9 months for the mitomycin plus gemcitabine group.

A phase II trial of chemoembolization was reported by Tellez et al (29), in which administration of cisplatin (10 mg/mL), doxorubicin (3 mg/mL), and mitomycin C (3 mg/mL) was followed by administration of bovine collagen material. In their prospective nonrandomized study, performed in a group of 30 patients, the authors achieved a median survival of 29 months after the initial diagnosis of metastasis in the liver and 8.6 months from the initial chemoembolization procedure. Our study results showed an overall median survival of 14 months after the first chemoembolization procedure. This difference in survival is probably attributed to the time between the interventions—in our protocol, we repeat the procedure every 4 weeks while Tellez et al (29) used a 6–8-week spacing protocol between interventions.

In a study by Leichman et al (30), 31 patients with colorectal liver metastases underwent hepatic arterial chemoembolization with a collagen suspension, doxorubicin, mitomycin C, and cisplatin, with systemic infusion of 5-fluorouracil chemotherapy and leucovorin weekly. In that study, one complete response and eight partial responses were observed, with a response rate of 29%. Results indicated that the 1-year survival rate was 58%, and the median survival time for the whole group was 14 months. These data almost coincide with our data (62% 1-year survival rate and 14-month median survival time), and on this basis it can be suggested that combined systemic and local chemotherapy achieved results similar to those with local chemotherapy alone. In addition, the local chemotherapy–only regimen carries the advantage of being less systemically toxic.

Voigt et al (31) achieved good results with tolerable toxicity when they performed chemoembolization by using a combination of mitomycin C, dexamethasone, and interferon alpha 2b mixed with degradable starch microspheres, followed by oxaliplatin, folinic acid, and 5-fluorouracil in case of liver metastasis of colorectal cancer metastases refractory to standard systemic chemotherapy. We agree with the results of Voigt et al regarding tolerability of treatment, since most of our patients tolerated the treatment well (apart from...
nausea and vomiting observed in some patients) and were discharged on the same day of the intervention.

Current ablation techniques such as LITT are effective in liver lesions. However, in large liver metastases (>5 cm in largest dimension), neoadjuvant therapy is necessary to reduce size in order to achieve a safety margin of 1 cm beyond the tumor to reduce the risk of residual tumors (32). LITT as a neoadjuvant treatment was performed in our study population for those patients who had five or fewer metastases, the largest of which was 5 cm or smaller in diameter. Ablation treatment was monitored by using MR imaging until complete ablation of the lesion (seen as signal loss in thermosensitive MR sequence) was achieved (33). Complete ablation was achieved in all patients of the neoadjuvant group. Thus, the combined treatment method of transarterial chemoembolization and LITT was used in the treatment of patients with unresectable liver metastases of colorectal cancer. Although the median survival rate among the neoadjuvant group treated with LITT after chemoembolization was not significantly increased versus the palliative group (Fig 6), we still think that LITT plays a role in terms of reducing the need for re-intervention.

Figures 4, 5

Figure 4: Survival data (Kaplan-Meier method) of patients with liver metastases of colorectal cancer (n = 463). Curve A: Median survival time from diagnosis of liver metastases was 38 months. Curve B: Median survival time was 14 months from the start of transarterial chemoembolization therapy.

Figure 5: Kaplan-Meier survival curve. Curve A: Survival data of 243 patients with liver metastases after transarterial chemoembolization with mitomycin C. Median survival was 14 months. Curve B: In 67 patients treated with mitomycin C and irinotecan, median survival was 14 months. Curve C: In 153 patients treated with mitomycin C and gemcitabine, median survival was 13.9 months.

Figures 6, 7

Figure 6: Kaplan-Meier survival curve. Median survival of the palliative group was 14 months; symptomatic group, 8 months; and neoadjuvant group, 17.6 months. Curve A: Survival data for neoadjuvant group (n = 60). Curve B: Survival data for palliative group (n = 335). Curve C: Survival data for symptomatic group (n = 68).

Figure 7: Kaplan-Meier survival curve. Local control results (RECIST criteria) were partial response, 14.7% of patients; stable disease, 48.2%; and progressive disease, 37.1%. Curve A: In patients with partial response, median survival was 18.2 months. Curve B: In patients with stable disease, median survival was 13.5 months. Curve C: In patients with progressive disease, median survival was 13 months.
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Our study had limitations. The study design was nonrandomized. There were also limited differences in the symptomatic and palliative indications for chemoembolization. Repeated studies have therefore shown that it might be possible to prolong survival in the treatment of metastatic colorectal cancer in the liver by means of regional chemotherapy (1). In summary, our results indicate that transarterial chemoembolization is an effective therapy for neoadjuvant, symptomatic, or palliative treatment in patients with colorectal cancer liver metastases.

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