

## Transcatheter therapy of gastric cancer metastatic to the liver: preliminary results

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**Abstract:** Little is known about the effectiveness of transcatheter chemotherapy in liver metastases from gastric cancer. The aim of this study was to evaluate the initial results of hepatic artery infusion and oily chemoembolization in these liver secondaries. Courses of transcatheter arterial infusion with 5-fluorouracil/doxorubicin (12 patients) and oily chemoembolization with doxorubicin-in-iodized oil and gelatin sponge (12 patients) were performed in 24 patients with histologically proven unresectable gastric cancer liver metastases. A positive effect of treatment (partial response + stabilization) was seen in 92% of the patients after chemoinfusion and in 50% after chemoembolization. The 1- and 2-year actuarial survival rates were 92% and 53% for infusion vs 50% and 17% for chemoembolization, respectively (log-rank test,  $P = 0.0009$ ). For patients who had already died, the mean survival was 19.2 months vs 9.5 months (Student's  $t$ -test,  $P < 0.05$ ) with median survivals of 23 months vs 8 months, respectively. The results with arterial infusion were very close to those reported for liver resection. Transcatheter therapy appears to be useful for the palliation of unresectable liver metastases from gastric cancer. If regional chemotherapy is used, arterial infusion should be the first-choice treatment, with oily chemoembolization being reserved for patients who do not respond to infusion.

**Key words:** gastric cancer, liver neoplasms, secondary, interventional radiology, chemotherapy, chemoembolization, therapeutic

### Introduction

Cancer of the stomach is one of the most common malignant tumors worldwide. In Russia, the frequency of this disease is second highest among all cancers.<sup>1</sup> Liver metastases appear in about 30% of the patients.<sup>2,3</sup>

Hepatic resection has been performed for metastatic liver cancer, resulting in improvement in prognosis and a low operative mortality. However, only 5% to 15% of patients, mostly those with hepatocellular carcinoma and colorectal liver metastases, can be radically operated.<sup>4,5</sup> The resectability of gastric cancer liver secondaries is unknown, because few surgeons have the experience of ten or more resections in this disease.<sup>2,3,6</sup>

Most patients presenting with liver metastases have inoperable disease. The survival of untreated patients is between 2 and 6 months.<sup>7,8</sup> Systemic chemotherapy is the treatment of choice for advanced gastric cancer, with the response rate being approximately 25%.<sup>9,10</sup> Radiation therapy has limited efficacy in most patients.<sup>2-5</sup> Interventional radiological treatment is useful for primary and some metastatic hepatic malignancies, but little is known about its effectiveness in gastric cancer metastatic to the liver.

The appropriate method for the management of nonresectable colorectal liver metastases is hepatic arterial infusion (HAI) or celiac artery infusion through a surgically or angiographically placed catheter.<sup>11</sup> Transcatheter oily chemoembolization (OCE) is widely used for the palliation of hepatocellular carcinoma and liver neuroendocrine metastases.<sup>12,13</sup> However, there are only a few reports in the literature that deal with intravascular therapy of hepatic metastases from gastric cancer.<sup>3,14-16</sup> The purpose of this study was to assess and compare the effectiveness of HAI and OCE in this morphologic form of metastasis.

## Subjects and methods

Between 1986 and 1999, 75 patients with liver metastases from gastric cancer were treated at our institution. Of these, 75 patients, 46 received systemic chemotherapy or symptomatic therapy because of contraindications to surgery and interventional radiologic treatment. In most of these patients, these contraindications included a tumor volume occupying more than 70% of the liver, or extrahepatic metastases.

Two patients received surgical treatment. One patient underwent curative right hepatectomy, while in the other patient, gastrectomy with simultaneous cytoreductive left hepatectomy was done.

Transcatheter therapy was performed in the 27 remaining patients with metachronous, multiple unresectable bilobar liver metastases. The primary tumor had been resected at our institution ( $n = 10$ ) or other hospitals ( $n = 17$ ) 4 to 36 months before. Patients with stage II or stage III gastric cancer (International Union against Cancer; UICC classification) received postoperative adjuvant systemic chemotherapy of 5-fluorouracil, 10 mg/kg per day given on 3 days every month.

HAI or OCE treatment was randomized in 24 patients (12 HAIs and 12 OCEs), using the envelope method. The 3 remaining patients, who received celiac artery infusion after unsuccessful attempts at selective catheterization of the hepatic artery, were excluded from the analysis.

### *HAI group*

There were six men and six women, aged 24–65 years (mean, 47 years) in the HAI group. The primary gastric tumor was adenocarcinoma in ten patients, squamous cell carcinoma in one patient, and undifferentiated carcinoma in one patient. Three patients were UICC stage IB, five were stage II, and four were stage IIIA. According to pretreatment computed tomography (CT), the volume of liver involvement was 20% to 50% (mean, 35%). No extrahepatic disease was found at the time of initiation of treatment in any patient.

### *OCE group*

The OCE group consisted of five men and seven women, aged 26–69 years (mean, 49 years). The primary tumor was gastric adenocarcinoma in all patients, with two patients being stage IB, seven, stage II, and three stage IIIA. Metastatic disease involved 15% to 50% (mean, 30%) of the liver.

Angiography was carried out as follows. The Seldinger technique was used for the catheterization of the femoral artery. Celiac and superior mesenteric

arteriography, using 5.0 to 5.5-F selective visceral catheters, was performed to define hepatic vascular anatomy, volume and location of the tumor, and portal vein patency.

All courses of HAI were performed using an angiographic approach. The proper hepatic artery was selectively catheterized. If variant hepatic arteries were present, the aberrant arteries, except for the one used for HAI, were embolized with steel coils. Infusion of 5-fluorouracil (1000 mg/m<sup>2</sup>) was given daily, for 4 days. On the fourth day, doxorubicin (40 mg/m<sup>2</sup>) was added as a bolus injection, and the catheter was removed.

In OCE, if both lobes of the liver were affected, the treatment was performed by separate selective right hepatic and left hepatic chemoembolization done at an interval of 1 week. When possible, the tip of the catheter was placed distal to the cystic artery. OCE was carried out by the intrahepatic injection of 30–80 mg of in 10–15 ml of Lipiodol Ultrafluid (Guerbet, Aulnay-sous-Bois, France), followed by hepatic artery occlusion with cubes (1 × 1 mm) or torpedoes (1 × 5 mm) of Gelfoam (Upjohn, Kalamazoo, MI, USA). Gentamycin (80–160 mg) was added to the embolization mixture.

Follow-up included clinical observation, laboratory analyses, bone scintigraphy, chest radiography, ultrasound examination, and CT or magnetic resonance imaging (MRI).

Both treatments were performed every 2 months for up to three cycles, then every 3–5 months, depending on effectiveness, evaluated by CT or MRI and the general condition of the patient. When the tumor volume exceeded 70% of the liver or extrahepatic metastases were detected, the locoregional treatment was stopped.

For statistical analysis, we used Kaplan-Meier estimation with log-rank test for comparison. The mean and median survivals for patients who died were calculated by Student's *t*-test.

## Results

### *HAI*

In total, 12 patients received 43 courses (range, 2 to 7 per patient) of HAI. No complete response was seen. After the first course, partial response, stabilization, and tumor progression were noted in 3 (25%), 8 (67%), and 1 (8%) patients, respectively. Complications included chemical hepatitis ( $n = 1$ ), duodenal ulcer ( $n = 1$ ), anemia ( $n = 2$ ), and were managed conservatively.

At present, eight patients are alive, including all three with primary partial response and five with stabilization. Seven patients show remission that has lasted for 3 months to 8 months, and one, who had received seven HAI procedures, has shown stabilization of metastases in the 60 months since the beginning of the treatment.

**Table 1.** Results of hepatic arterial infusion (HAI) and oily chemoembolization (OCE) in patients with unresectable liver metastases from gastric cancer

Treatment	Mean survival (months) <sup>a</sup>	Median survival (months) <sup>a</sup>	Survival (%)	
			1 Year	2 Years
HAI	19.2 ± 6.3	23.0	92	53
OCE	9.5 ± 4.3	8.0	50	17

<sup>a</sup>For those patients who died

Of the four patients who died, two died of progression of liver metastases and two of lung metastases, 8 to 26 months after the beginning of the HAI treatment (mean, 19.2 ± 6.3 months); the median survival was 23 months (Table 1).

### OCE

Twelve patients received 43 OCEs (range, 1 to 6 per patient). Partial tumor response, stabilization, and progression of metastases were seen in 1 (8%), 5 (42%), and 6 (50%) patients, respectively.

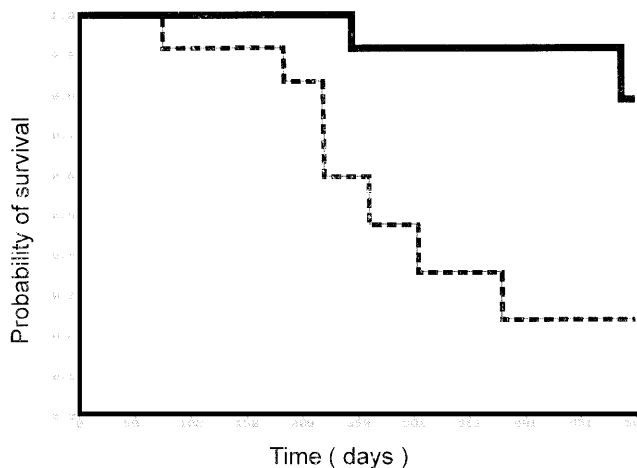
Post-embolization syndrome, which occurred in all patients, included right upper quadrant pain, fever, and nausea. These symptoms disappeared within 5 days with symptomatic therapy. There was one serious complication: the patient developed bile duct necrosis with the formation of multiple bilomas. Treatment with percutaneous transhepatic biliary drainage was successful.

At present, four patients are alive; three patients (all of whom showed stabilization after the first OCE) have shown remission of 3 to 7 months' duration, and one patient, who showed a partial response, is alive 69 months after the first of four OCEs. Eight patients (six with progression and two with stable disease) died 2 to 17 months (mean, 9.5 ± 4.3 months) after the beginning of the OCE treatment; median survival was 8 months (Table 1). The causes of death were progression of liver metastases ( $n = 5$ ) and spread of the tumor ( $n = 3$ ).

The 1- and 2-year probabilities of survival for the HAI vs the OCE group were 92% and 53% vs 50% and 17%, respectively (log-rank test;  $P = 0.0009$ ) (Fig. 1). Also, the mean survival of patients who had already died was significantly better after HAI than after OCE (Student's  $t$ -test;  $P < 0.05$ ) (Table 1).

### Discussion

The data in the literature show that radical hepatic surgery is rarely possible in patients with gastric cancer metastatic to the liver; few centers have experience with ten or more curative resections.<sup>2,3,6</sup> In our clinic, only



**Fig. 1.** Probability of survival of patients with gastric cancer liver metastases after hepatic arterial infusion (continuous line;  $n = 12$ ) vs oily chemoembolization (dashed line;  $n = 12$ );  $P = 0.0009$

two resections of gastric cancer metastases have been performed, one curative and one cytoreductive.

Unfortunately, even if all visible metastases are resected, the prognosis is still usually poor. Bines et al.<sup>6</sup> reported a mean survival of 8 months after the simultaneous resection of gastric cancer and synchronous liver metastases. Miyazaki et al.<sup>2</sup> reported a mean survival of 10 months after curative hepatic surgery, with only 1 of 21 patients alive more than 5 years after the surgery. Taking into account both the individual experience and the data in the literature, many surgeons consider hepatic resection to be inadvisable for gastric cancer metastases.<sup>8,17,18</sup>

The main cause of these unsatisfactory results is the peculiar biology of the metastatic malignant tumor. It is known that one detected metastasis is followed by three to five micrometastases.<sup>19</sup> Moreover, gastric cancer secondaries quickly invade the lungs, peritoneum, and other organs, and often cause death without recurrence in the resected liver.<sup>3,8</sup> Potentially, the results of surgery can be improved with a combination of resection and transcatheter treatment: one of our patients developed recurrence of metastases 9 months after right

hepatectomy and responded to HAI, surviving for 31 months, while the other patient also received HAI, and died 17 months after the cytoreductive resection.

At present, there is increased interest in the locoregional treatment of liver secondaries, but little is known about the results of HAI and OCE in gastric cancer liver metastases. In an earlier report, we found that mechanical embolization of the hepatic artery prolonged survival for some patients.<sup>15</sup> Arai et al.<sup>14</sup> performed HAI in 34 patients using an implantable port system and combination chemotherapy with 5-fluorouracil, doxorubicin, and mitomycin C. The response rate (complete plus partial) in the evaluated patients was 73%, and the overall median survival was 15 months. Taniguchi et al.<sup>3</sup> reported a 9-month mean survival and 45% 1-year survival after HAI with 5-fluorouracil and carboplatin in patients who had liver metastases from gastric cancer. Saikawa et al.<sup>16</sup> described a patient with advanced non-resected gastric cancer and liver metastases who was alive 17 months after celiac artery infusion with mitomycin C and cisplatin.

Our results also show that intraarterial chemotherapy plays a role in the palliation of unresectable gastric cancer liver metastases. Treatment with HAI or OCE was possible in about one-third of all patients coming to our clinic. The mean survival after transcatheter management was comparable to that for curative surgery. The 1-year actuarial survival was 71% (92% for HAI and 50% for OCE), and there were 2 (8%) 5-year survivors. The prognosis was directly correlated with tumor response to the treatment.

The major advantage of transcatheter treatment is its minimal invasiveness. All procedures were performed under local anesthesia. There was no mortality. Serious complication (bile duct necrosis) developed in only one (4%) patient and was successfully treated by percutaneous drainage without laparotomy.

Alternative methods of local treatment for liver metastases include cryosurgery,<sup>20</sup> percutaneous ethanol injection therapy,<sup>21</sup> radio-frequency ablation,<sup>22</sup> and laser-induced thermodestruction.<sup>23</sup> These treatments induced 70%–90% tumor necrosis and resulted in temporary remission of the disease, but the long-term results have yet to be determined. Taking into account the presence of micrometastases, many authors have combined local treatment with regional chemotherapy such as HAI or OCE.<sup>24,25</sup>

In conclusion, transcatheter therapy appears to be safe and effective for the palliation of unresectable liver metastases from gastric cancer. In our small series of patients, the effectiveness of HAI was superior to that of OCE, probably because of the greater sensitivity of gastric cancer to chemotherapy. We can state that, if regional chemotherapy is used, HAI should be the first

treatment, rather than OCE, which may be reserved for patients who do not respond to infusion. In future, we plan to use arterial infusion via an implantable port system in patients who show a positive response to angiographic HAI.

We believe that progress can be achieved with transcatheter therapy, taken together with the successes of pharmacology and immunotherapy. Also, a multimodal approach to the treatment of this disease is recommended.

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