

# Regional Chemotherapy via Transarterial Chemoembolisation in Colorectal Liver Metastases

a report by

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Transarterial chemotherapy has shown its efficacy in local tumour control and in improving quality of life, symptomatic control and survival time in hepatic malignancies. We intend to provide an overview of the techniques, indications and results of transarterial chemoembolisation (TACE) of hepatic colorectal metastases. This treatment approach is performed in symptomatic, palliative, adjuvant and potentially curative intentions. The most recent studies, including TACE of colorectal liver metastases, will be presented and discussed. However, variations of inclusion criteria and treatment regimens used in the different studies led to a discrepancy in the results. The overall median survival is between nine and 62 months and the morphological response is between 14 and 76%. The future role of this therapy will also be discussed in this article.

The liver may be the only metastatic site in patients with colorectal carcinoma. Liver metastases can be found in up to 80% of these patients; up to 50% of these cases are identified at primary presentation.<sup>1,2</sup> Surgical resection is the standard curative treatment, but fewer than 20% of patients are candidates for this surgery. Recent series have shown five-year survival rates of 25–37% and 10-year survival rates of 20–22%. Recurrences are encountered in 65–80% of patients, and 50% of these occur in the liver.<sup>3</sup>

Systemic chemotherapy has been the standard treatment in patients with unresectable and/or extrahepatic spread for over 40 years. Treatment with 5-fluorouracil (5-FU) resulted in a response rate of 20% and a two-year survival rate of 20%. Adding irinotecan or oxaliplatin to 5-FU-based regimens resulted in superior response rates (40–57%) and longer median survival times (15–20 months),<sup>3–6</sup> whereas irinotecan and capecitabine yielded tumour control in 61% of patients.<sup>7</sup>

Alternative treatment options have been investigated to improve outcomes in patients with metastatic colorectal cancer. One of these treatment options is percutaneous local tumour destruction utilising radiofrequency ablation (RFA), laser-induced thermotherapy (LITT), cryotherapy, microwave therapy or percutaneous alcohol injection.<sup>8</sup> In the largest published patient series so far, LITT was performed in 603 patients with liver metastases. The one-, two-, three- and five-year survival rates

were 94, 77, 56 and 37%, respectively, while the median survival was 3.5 years.<sup>9</sup> RFA showed a three-year survival rate of 47% in 117 patients with liver metastases.<sup>10</sup> The overall morbidity of such procedures ranges between 0.1 and 2.5%, and the mortality rate is less than 1%.<sup>8</sup>

Another treatment option is the transarterial administration of chemotherapeutic agents, either alone as a hepatic arterial infusion (HAI) or combined with vascular embolising material (TACE). Bland vascular embolisation (TAE) can also be applied.

## Transarterial Chemoembolisation

### Indications

Systemic chemotherapy with 5-FU, leucovorin and oxaliplatin (FOLFOX) or Xeloda® plus oxaliplatin (XELOX) should be used in patients with potentially resectable liver metastases. TACE can be performed as a neoadjuvant therapeutic regimen aiming at reducing lesion size and thus making surgery or thermal ablation feasible. In this way, non-resectable lesions can be converted to resectable ones. On the other hand, it can be used as a palliative measure in cases of extrahepatic spread or post-surgical recurrence, or as a symptomatic treatment, for example in cases of hormone-secreting metastases or painful capsular invasion. The contraindications to this therapy are operability, extensive liver involvement (more than 75%), liver insufficiency, myelodepression and brain metastases. Portal vein occlusion is considered to be a relative contraindication. Patients with a tumour involvement of more than 75% of the liver may not benefit from TACE due to the development of major complications, whereas patients with a tumour burden of less than 50% and higher (>50%) lipiodol uptake show a trend towards longer survival.<sup>11,12</sup> Hence, significant liver toxicity can be a limiting factor that compromises the safety of such a procedure.<sup>13</sup> Extrahepatic metastases are a known limitation to the use of TACE. The extent of liver involvement by metastatic lesions can be another limitation.

### Technique and Complications

Embolising agents used in TACE can have either a temporary effect (usually microspheres, degradable starch microspheres [DSM] and Gelatine sponge) or a permanent effect (polyvinyl alcohol). Lipiodol, in addition to its microvascular occlusive effect, has a special affinity to be uptaken and retained by hepatic tumour cells. Thus, when it is emulsified with cytotoxic drugs it significantly enhances their effect.<sup>14</sup>

There are several chemotherapeutic agents used in TACE. Mitomycin C (Medac, Hamburg, Germany) is the most consistently applied agent, and is usually administered as an emulsion with lipiodol due to its high local effectiveness. After sterile preparation, a 4–5F sheath is



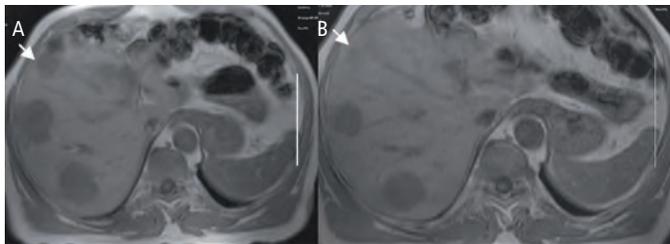
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**Table 1: Methods and Results of Transarterial Chemoembolisation in Patients with Colorectal Liver Metastases During the Past Three Years**

| Study                | n  | Sessions | Anticancer Drug                                      | Embolising Material | Morph. Response | Median Survival          |
|----------------------|----|----------|--|---------------------|-----------------|--------------------------|
| Wasser <sup>12</sup> | 21 | 3.4      | Mitomycin  | Starch (DSM)        | 14%             | 13.8 month               |
| Muller <sup>16</sup> | 66 | 4.5      | Melphalan<br>(5-FU and<br>GM-CSF)                    | Lipiodol<br>Gelfoam | 76.6%           | Not reached <sup>a</sup> |
| Popov <sup>13</sup>  | 11 | 1        | Mitomycin  | Gelfoam             | N/A             | 9 months                 |
| Voigt <sup>27</sup>  | 10 | 4.3      | Mitomycin<br>Interferon<br>(oxaliplatin<br>and 5-FU) | Starch (DSM)        | 50%             | Not reached <sup>b</sup> |

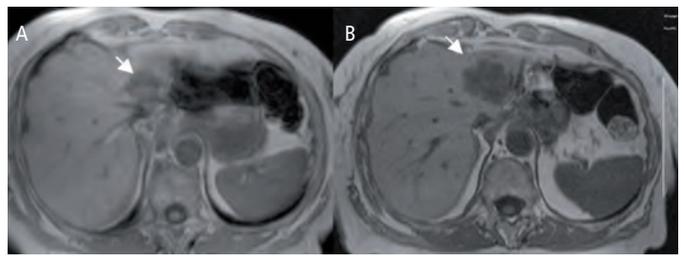
a. Median survival was not reached after an observation period of 28 months; b. Four patients still underwent treatment by the time of publication. GM-CSF = granulocyte-macrophage colony-stimulating factor; DSM = degradable starch microspheres.

**Figure 1: Magnetic Resonance Imaging Axial T1-weighted Image of the Liver Showing Multiple Colorectal Metastatic Lesions**

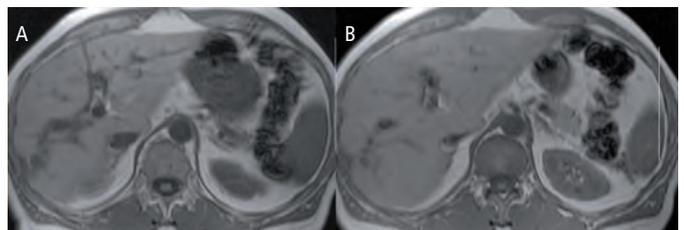
A: Multiple colorectal metastatic lesions were treated by six transarterial chemoembolisation sessions. B: A partial response was seen in a post-treatment magnetic resonance imaging (MRI) study according to the Response Evaluation Criteria In Solid Tumours (RECIST). The sum of maximum diameters of all the lesions showed more than a 50% reduction. The most anterior lesion showed almost complete regression (arrow).

introduced into the femoral artery through which a 4–5F pigtail catheter is advanced to the abdominal aorta. An angiographic survey of the abdominal vessels is performed. Mesenteric arteriography is then performed using a 4–5F Cobra or Sidewinder I or III catheter to look for the presence of right hepatic artery variants and for indirect portography during the venous phase. A 4–5F Cobra catheter or Sidewinder is placed in the coeliac trunk and advanced into the proper hepatic artery distal to the origins of gastroduodenal and right gastric arteries. Depending on size, location and arterial supply to the tumour, the tip of the catheter can be advanced further into the segmental arteries. When selective or super-selective catheterisation is problematic, a 3F microcatheter can be used. After embolisation, devascularisation is confirmed by an additional angiographic study of the hepatic artery. At least three courses of repeated chemoembolisation should be performed at four-week intervals. The treatment can be performed further over a longer course in case of satisfactory morphological response.

The most common complication that is associated with TACE is 'post-embolisation syndrome' or 'tumour lysis syndrome', which consists of pain in the right upper quadrant, nausea, vomiting and mild transient or persistent fever, as well as elevation of liver enzymes. This occurs in 3.8–15% of all interventions.<sup>12,15</sup> Compared with TACE with long or permanent arterial occlusion, the post-embolisation syndrome seems to be less pronounced using temporary embolising material such as DSM. Hence, temporary embolising material is generally considered to be more suitable in TACE performed as a palliative

**Figure 2: Progressive Disease Despite Transarterial Chemoembolisation**

A: Magnetic resonance imaging (MRI) axial T1-weighted image of the liver showing a colorectal metastatic lesion of the left lobe (arrow); B: Post-treatment MRI. A distinct increase in size is seen.

**Figure 3: Magnetic Resonance Imaging Axial T1-weighted Image of the Liver**

A: Magnetic resonance imaging (MRI) axial T1-weighted image of the liver showing a colorectal metastatic lesion of the right lobe (arrow); B: Post-treatment MRI. Some decrease in size was noted, but this decrease was less than 50%, and thus this case was categorised as stable disease according to Response Evaluation Criteria In Solid Tumours (RECIST).

treatment.<sup>12</sup> Moreover, it is not feasible to permanently occlude all the feeding arteries at the expense of liver blood supply in extensive metastases involving both lobes. More serious but relatively less common complications are liver abscess, infarction, tumour rupture and acute liver failure. Pulmonary complications include lipiodol embolism, which is symptomatic in only 2–4% of cases.<sup>15</sup>

## Results

TACE treatment of colorectal cancer metastases was evaluated in several studies, the results of which are shown in Table 1 and Figures 1–3. One of the studies showed the most favourable responses to this treatment, with patients achieving complete response (CR) in 10% of cases, partial response (PR) in 42.4% of cases, stable disease (SD) in 18.2% of cases and no response (NR) in 12.1% cases. The two-year survival rate was 66%. There was no statistically significant difference between chemo-naïve patients and patients pretreated by any kind of systemic therapy.<sup>16</sup>

Transarterial embolisation without cytotoxic drugs can achieve equally satisfactory results.<sup>17,18</sup> Three randomised controlled trials elaborated on this point by comparing TACE and TAE in colorectal liver metastases. Patients were randomised to either TACE or TAE. There was a slightly higher median survival in the TACE arm that did not reach statistical significance. No statistically significant difference between the two arms was noted in local tumour response.<sup>19–21</sup> Thus, the main limiting factor to the use of embolisation is the extent of liver involvement, which defines the possible degree of vascular compromise. In bilobar extensive lesions, hepatic artery infusion is more feasible. In more localised lesions it would be useful to add embolisation to regional chemotherapy in order to achieve a better outcome, especially in cases of hypervascular metastases as renal cell

carcinoma secondaries. Embolisation is also useful in the presence of an associated vascular lesion such as arteriovenous (AV) malformation, fistulae or haemangioma.

## Discussion

The available data allow us to draw some important conclusions. The median survival rate observed in colorectal metastases in most studies using regional chemotherapy ranges between 28 and 46 months and is lower than that achieved by surgical resection.<sup>22</sup> A possible explanation is that surgical patients have more favourable liver and general condition, and that earlier tumour stages are assigned to surgery. A small percentage of patients are eligible for surgery

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and a high recurrence rate is expected, as mentioned earlier.<sup>3,22</sup> Besides, operative morbidity and mortality can reach up to 39 and 5%, respectively.<sup>22</sup>

However, instead of comparing the advantages and disadvantages of TACE and surgery, we should discuss their complementary and supplementary roles. TACE increases the possibility of surgery, improves its outcome and can be used when surgery is not possible or not successful. In inoperable patients, TACE and percutaneous

ablation can have a similar outcome. TACE achieves downsizing of metastases so that patients become eligible for thermal ablation.<sup>23,24</sup> If the metastasis progresses beyond the inclusion criteria for ablation, TACE can provide an alternative. We applied this combined approach to 162 patients with metastatic lesions larger than 5cm. A significant decrease in lesion size was achieved in 82 patients, who were then shifted to image-guided laser ablation. In cases of disease progression, TACE was continued or systemic chemotherapy was applied.<sup>25</sup>

Systemic and transarterial chemotherapy can be applied simultaneously or can replace one another. Systemic treatment is required if extra-hepatic metastases are present. As seen in *Table 1*, the results achieved by TACE regarding response rate and median survival times can surpass those of systemic chemotherapy, as mentioned earlier, and can also avoid the systemic side effects of the latter.<sup>3,26</sup>

We can safely assume that the effectiveness of the various embolising materials and cytotoxic drugs was not adequately compared in the studies available due to the difference in primary tumours, treatment regimens, doses and intra- or extra-hepatic extent of the metastases in different studies. This can be performed in a series of dedicated randomised trials using two or more agents to avoid selection bias and to limit the influence of any confounding factors. This will provide a more comprehensive and accurate view of the most effective treatment combinations.

## Conclusion

Regional chemoembolisation of liver metastases in colorectal cancer is an effective symptomatic and palliative treatment. More research and work must be directed towards the prospective analysis of its neoadjuvant and curative role. ■

- Pickren JW, Tsukada Y, Lane WW, Liver metastasis. In: Weiss L, Gilbert HA (eds), *Analysis of Autopsy Data*, Boston: GK Hall and Company, 1982;2–18.
- Vogl TJ, Zangos S, Balzer JO, et al., Transarterial chemoembolization of liver metastases: Indication, technique, results, *Roefo*, 2002;174:675–83.
- Cohen AD, Kemeny NE, An update on hepatic arterial infusion chemotherapy for colorectal cancer, *Oncologist*, 2003;8:553–66.
- Ji SH, Park YS, Lee J, et al., Phase II study of irinotecan, 5-fluorouracil and leucovorin as first-line therapy for advanced colorectal cancer, *Jpn J Clin Oncol*, 2005;35(4):214–17.
- Kuehr T, Ruff P, Rapoport BL, et al., Phase III study of first-line irinotecan combined with 5-fluorouracil and folinic acid Mayo Clinic schedule in patients with advanced colorectal cancer, *BMC Cancer*, 2004;4:36.
- Kemeny N, Garay CA, Gurtler J, et al., Randomized multicenter phase II trial of bolus plus infusional fluorouracil/leucovorin compared with fluorouracil/leucovorin plus oxaliplatin as third-line treatment of patients with advanced colorectal cancer, *J Clin Oncol*, 2005;22(23):4753–61. Erratum in: *J Clin Oncol*, 2005;23(1):248.
- Hofheinz RD, Gnad-Vogt U, Wein A, et al., Irinotecan and capecitabine as second-line treatment after failure for first-line infusional 24-h 5-fluorouracil/folinic acid in advanced colorectal cancer: a phase II study, *Anticancer Drugs*, 2005;16(1):39–45.
- Germer CT, Buhr HJ, Isbert C, Non-operative ablation for liver metastases. Possibilities and limitations as a curative treatment, *Chirurg*, 2005;76:552–63.
- Vogl TJ, Straub R, Eichler K, et al., Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy – local tumor control rate and survival data, *Radiology*, 2004;230:450–58.
- Solbiati L, Livraghi T, Goldberg SN, et al., Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients, *Radiology*, 2001;221:159–66.
- Kress O, Wagner HJ, Wied M, et al., Transarterial chemoembolization of advanced liver metastases of neuroendocrine tumors—a retrospective single-center analysis, *Digestion*, 2003;68(2–3):94–101.
- Wasser K, Giebel F, Fischbach R, et al., Transarterial chemoembolization of liver metastases of colorectal carcinoma using degradable starch microspheres (Spherex): personal investigations and review of the literature, *Radiologe*, 2005;45(7):633–43.
- Popov I, Lavrnic S, Jelic S, et al., Chemoembolization for liver metastases from colorectal carcinoma: risk or a benefit, *Neoplasma*, 2002;49(1):43–8.
- Ohtsuka Y, Matsunaga T, Yoshida H, et al., Optimal strategy of preoperative transcatheter arterial chemoembolization for hepatoblastoma, *Surg Today*, 2004;34(2):127–33.
- Fiorentini G, Rossi S, Bonechi F, et al., Intra-arterial hepatic chemoembolization in liver metastases from neuroendocrine tumors: a phase II study, *J Chemother*, 2004;16(3):293–7.
- Muller H, Nakchbandi V, Chatzisavvidis I, von Voigt C, Repetitive chemoembolization with melphalan plus intra-arterial immuno-chemotherapy within 5-fluorouracil and granulocyte-macrophage colony-stimulating factor (GM-CSF) as effective first- and second-line treatment of disseminated colorectal liver metastases, *Hepatogastroenterology*, 2003;50(54):1919–26.
- Schell SR, Camp ER, Caridi JG, Hawkins IF Jr, Hepatic artery embolization for control of symptoms, octreotide requirements, and tumor progression in metastatic carcinoid tumors, *J Gastrointest Surg*, 2002;6(5):664–70.
- Loewe C, Schindl M, Cejna M, et al., Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and lipiodol: assessment of mid- and long-term results, *AJR Am J Roentgenol*, 2003;180(5):1379–84.
- Hunt TM, Flowerdew AD, Birch SJ, et al., Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases, *Br J Surg*, 1990;77(7):779–82.
- Martinelli DJ, Wadler S, Bakal CW, et al., Utility of embolization or chemoembolization as second-line treatment in patients with advanced or recurrent colorectal carcinoma, *Cancer*, 2004;74(6):1706–12.
- Salman HS, Cynamon J, Jagust M, et al., Randomized phase II trial of embolization therapy versus chemoembolization therapy in previously treated patients with colorectal carcinoma metastatic to the liver, *Clin Colorectal Cancer*, 2002;2(3):173–9.
- Yoon S, Tanabe K, Surgical treatment and other regional treatments for colorectal cancer liver metastases, *Oncologist*, 1999;4(3):197–208.
- Vogl TJ, Mack MG, Balzer JO, et al., Liver metastases: neoadjuvant downsizing with transarterial chemoembolization before laser-induced thermotherapy, *Radiology*, 2003;229(2):457–64.
- Maataoui A, Qian J, Mack MG, et al., Liver Metastases in Rats: Chemoembolization Combined with Interstitial Laser Ablation for Treatment, *Radiology*, 2005;237:479–84.
- Vogl TJ, Mack MG, Balzer JO, et al., Liver metastases: neoadjuvant downsizing with transarterial chemoembolization before laser-induced thermotherapy, *Radiology*, 2003;229(2):457–64.
- Barber FD, Mavligit G, Kurzrock R, Hepatic arterial infusion chemotherapy for metastatic colorectal cancer: a concise overview, *Cancer Treat Rev*, 2004;30(5):425–36.
- Voigt W, Behrmann C, Schlueter A, et al., A new chemoembolization protocol in refractory liver metastasis of colorectal cancer: A feasibility study, *Onkologie*, 2002;25(2):158–64.