Treatment of liver metastases of colorectal cancer

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Introduction

Colorectal cancer is one of the most common malignancies, with ~1 million new cases and half a million deaths each year worldwide [1]. The development of metastases is the main cause of death. Liver metastases are diagnosed in 10–25% of patients at the time of resection of their primary colorectal tumor and, eventually, up to 70% of patients with colorectal cancer develop liver metastases [2, 3]. Without treatment, life expectancy for patients with colorectal metastases is poor and ranges from 5 to 9 months [4–6]. When the metastases are confined to the liver, which is the case in ~30% of the patients [7], there are several locoregional treatment options, including partial hepatic resection, local ablative therapy, administration of chemotherapy by hepatic artery infusion, systemic chemotherapy and isolated hepatic perfusion (IHP) with high-dose chemotherapy. If patients are ineligible for locoregional treatment, systemic chemotherapy is the only treatment option for metastatic colorectal cancer.

Resection

Hepatic resection is the gold standard in the treatment of colorectal liver metastases, and currently is the only curative treatment. Patients are eligible for hepatic resection if complete resection of colorectal metastases is possible with tumor-free margins and the remaining functional hepatic volume is sufficient to ensure adequate postoperative liver function. Patients with extrahepatic metastases are ineligible for hepatic resection, unless these metastases can be radically resected as well. Several studies have demonstrated that resection of simultaneous and sequential colorectal liver and lung metastases prolong survival of these patients [8, 9]. A selective group of patients who cannot undergo curative surgery for liver metastases because the remaining functional hepatic volume is too small can be treated preoperatively by selective embolization of portal vein branches [10]. The subsequently induced hypertrophy of the liver increases the functional hepatic volume and may allow a safe hepatic resection.

In recent years hepatic resection has proven to be a safe procedure. Morbidity after hepatic resection is limited and a mortality of <5% is repeatedly reported. Several large series have reported long-term survival rates and even cure after hepatic resection, with a median survival after radical hepatic resection ranging from 33 to 46 months, and 5-year survival rates ranging from 25% to 39% [11–13] (Table 1).

The role of adjuvant systemic chemotherapy after curative hepatic resection is unclear. No major randomized studies reporting disease-free and overall survival have yet been published. The European Organization for Research and Treatment of Cancer (EORTC) is running a multi-institutional, intergroup, randomized prospective trial (EORTC protocol 40983) to study the impact of pre- and postoperative 5-fluorouracil (5-FU)/leucovorin and oxaliplatin treatment on disease-free and overall survival in patients with resectable metastases. Similar to adjuvant oxaliplatin-based systemic therapy for primary colorectal cancer (MOSAIC trial) [20], this study may result in an increased disease-free survival.

There are several prognostic indicators that correlate with recurrence of liver metastases and survival. The most important indicator is involvement of the resection margin by tumor. Generally, a free surgical margin of at least 1 cm is recommended. A resection margin <1 cm is significantly correlated with a worse survival [13]. A hepatic resection with positive resection margins is considered to be non-curative and does not prolong patient survival compared with patients without a hepatic resection [13, 17]. Other important factors with a significant predictive value for patient survival are the tumor–node–metastasis stage of the primary tumor, the disease-free interval, the number and size of metastases, the presence of lymph node metastases in the liver hilus, and the preoperative carcinoembryonic antigen level [13, 14, 17, 18, 21].

Unfortunately, radical surgical resection of liver metastases is only possible in 10–25% of patients with colorectal metastases confined to the liver. In most patients the number, localization and/or size of the liver metastases or poor hepatic reserve preclude radical hepatic resection [13]. Furthermore, the majority of patients develop new, non-resectable hepatic or extrahepatic metastases after hepatic resection [12, 17, 22]. For these patients, no other curative treatment is currently available, but other treatment modalities, including local ablative therapy, systemic chemotherapy, hepatic artery infusion (HAI) and IHP can offer palliation and prolongation of disease-free and overall survival.

Local ablative therapy

Several modalities have been developed for local treatment of liver tumors, including cryotherapy, radiofrequency ablation (RFA), percutaneous ethanol injection, laser and photodynamic therapy. Among the local treatment options, RFA...
and cryoablation are the most commonly used treatment modalities [23].

For a cryoablation procedure, a cryoprobe with internally circulating liquid nitrogen is inserted in the lesion, repeatedly freezing and thawing the surrounding tumor tissue. The resulting formation of intra- and extracellular ice crystals causes tumor destruction. A median survival of ~26 months has been reported [24, 25]. However, cryoablation is associated with considerable morbidity, ranging from 10% to 30% [26, 27].

During RFA, an electrode delivers a high-frequency alternating current to the tissue, causing hyperthermia and finally inducing coagulative necrosis. RFA electrodes are either single rigid probes, inducing a cylindrical necrotic lesion, or multi-tined expandable electrodes that induce a spherical lesion. Similar to resection, an adequate margin surrounding the tumor should be achieved by RFA. This often necessitates multiple insertions when tumors are >3 cm in diameter, and emphasizes the pivotal importance of correct electrode placement. The probe is preferably placed under ultrasound or computed tomography guidance, either percutaneously or in an open procedure. The latter may be preferred when correct placement of electrodes is hindered (large tumors, compromised electrode accessibility) or when there is an increased risk of complications by the electrode placement itself (tumors close to large vessels, diaphragm or to adjacent internal organs). Additionally, RFA can be performed in combination with resection when the distribution of liver tumors prevents surgical removal of all lesions. Thus, RFA broadens the applicability of resection, enabling potentially curative treatment in more liver metastases patients. In recent years, RFA rather than cryoablation has been preferred by most clinicians and is therefore increasingly used. RFA is associated with lower recurrence rates and with considerably less procedure-related complications and mortality [28–30]. Furthermore, RFA is a less demanding and less costly procedure that can be performed percutaneously or laparoscopically in a safe manner, thereby avoiding a laparotomy [31].

High complete response rates of 52–95% are achieved by RFA [32–34]. It can offer palliation by prolongation of disease-free and overall survival to respectively 50% and 94% at 1 year [35], with a median survival time of 30–34 months. The results appear to be better in patients with small lesions, with treatment of larger lesions being associated with higher local recurrence rates [34, 36, 37]. RFA may result in cure although, at present, the limited follow-up time in most studies does not allow an accurate determination of the efficacy of RFA. Until further research is available comparing RFA with conventional surgery, resection is still considered to be the gold standard therapy for colorectal liver metastases. Currently, the EORTC is running a randomized phase III study of local treatment of liver metastases by radiofrequency with or without additional resection of resectable lesions combined with chemotherapy versus chemotherapy alone in patients with unresectable colorectal liver metastases (CLOCC trial, EORTC protocol 40 004).

### Regional chemotherapy

HAI of chemotherapy for the treatment of liver tumors is based on the principle that, in contrast to normal liver parenchyma, established colorectal liver metastases derive most of their blood supply from the hepatic artery [38, 39]. As a result, high drug concentrations can be achieved at the tumor site while the liver parenchyma is relatively spared. Furthermore, the liver metabolizes many cytotoxic drugs, such as fluorodeoxyuridine (FUDR), thereby reducing systemic exposure and, thus, toxicity is limited.

Several randomized studies involving HAI with FUDR or 5-FU have reported significantly higher tumor response rates compared with systemic administration (HAI 41%, systemic 14%; P < 0.0001) [40–43]. However, meta-analysis combining the results of seven randomized trials reported no significant survival benefit, while treatment-related hepatoxicity was considerable [44]. A recent randomized study in which 290 patients were included also did not show significant differences in tumor response, progression-free survival and overall survival between patients who had received 5-FU/leucovorin either systemically or by HAI, while the HAI group reported a worse quality of life compared with the systemically treated group [45]. As HAI for the treatment of colorectal metastases has failed to show a clear survival benefit compared with
systemic chemotherapy and is associated with serious complications, HAI is not considered a standard treatment and has only been used in clinical trials.

Systemic chemotherapy

For most patients with colorectal metastases, systemically administered chemotherapy is the only treatment option. Until recently, the standard first-line treatment for metastatic colorectal carcinoma consisted of 5-FU-based schedules. In most regimens, 5-FU is combined with leucovorin, resulting in response rates of ~20% and a median overall survival of ~12 months [46, 47].

In the past years several new agents have become available for first-, second- and third-line treatment of advanced colorectal cancer, such as irinotecan and oxaliplatin. Irinotecan in combination with 5-FU/leucovorin has proven to be superior in terms of progression-free survival, survival and quality of life compared with 5-FU/leucovorin alone in both first- and second-line therapy [48–51]. Similarly, combination of oxaliplatin with 5-FU/leucovorin, also showed an improved response rate, progression-free survival period and overall survival in both first- and second-line therapy [52–54]. Several studies have been undertaken treating patients with regimens with 5-FU/leucovorin, irinotecan and oxaliplatin. The first results show a median survival of up to 21.5 months, irrespective of the treatment sequence [55].

Recently, Cunningham et al. [56] reported that treatment with cetuximab, a chimeric monoclonal antibody directed against epidermal growth factor receptor (EGFR), of patients with EGFR-positive, irinotecan-refractory colorectal metastases demonstrated significant clinical activity in terms of
disease control and progression-free survival, especially when combined with irinotecan. Hurwitz et al. [57] showed that the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, to bolus IFL-chemotherapy (irinotecan, 5-FU, leucovorin) as first-line therapy for patients with colorectal metastases resulted in increased survival, progression-free survival, response rate and duration of response when compared with bolus IFL-chemotherapy alone.

Isolated hepatic perfusion

IHP involves a method of complete vascular isolation of the liver to allow local treatment of the liver. During this procedure the blood circulation of the liver is isolated from the systemic circulation. This is achieved by inserting inflow catheters in the common hepatic artery and the portal vein and an outflow catheter in the infrahepatic caval vein while the suprahepatic caval vein is occluded by a surgical clamp. The catheters are subsequently connected to a heart–lung machine and the anticancer drug is administered in this isolated circuit. After perfusion of the liver with the drug for a certain period of time (1 h in most IHP trials), the liver is flushed with 'clean' perfusate to wash out the anticancer drug, after which the natural blood circulation is restored [58].

The major advantage of IHP is the ability to treat the liver with drug levels that would be toxic if administered systemically. The dose of anticancer drugs that can be used is up to four-fold the maximum systemically tolerated dose, since vital organs are isolated from the perfusion circuit [58, 59]. Furthermore, effective antitumor compounds that cannot be administered systemically because of their toxicity, such as tumor necrosis factor (TNF)-α, can be used in IHP [60, 61]. Finally, hyperthermia can be applied by heating the perfusate solution, which is known to enhance antitumor efficacy of several anticancer drugs [62, 63].

IHP has been proposed as treatment modality for different kinds of non-resectable liver tumors [64, 65], but most experience has been obtained with colorectal liver metastases. The main selection criteria for IHP are essentially the same as used for hepatic resection, but with the additional criterion that the liver metastases cannot be resected or treated by local ablative therapy. The IHP technique with many variations has been used in studies with 5-FU [64, 66], mitomycin C [59, 67], cisplatin [64] and melphalan, with or without TNF-α [58, 60, 61, 64, 67–70] (Table 2). In most studies, mild hyperthermia up to 40°C is applied during IHP; hyperthermia alone (42.0–42.5°C) has been applied in only one study [71].

Recent clinical studies have mainly employed IHP with melphalan. Melphalan is an alkylating agent with a steep dose–response curve that is effective against colorectal cancer after a relatively short exposure time and is therefore a very interesting drug for IHP [72, 73]. Alexander and colleagues [61, 68] have reported IHP studies with different treatment strategies, including IHP with high doses of melphalan alone and moderately high doses of melphalan combined with TNF-α or followed by monthly hepatic intra-arterial infusion of FUDR and leucovorin. Results of these studies show response rates up to 74%, a median time to progression up to 14.5 months and a median survival of 27 months. Similar results were achieved with higher doses melphalan without TNF-α at the Leiden University Medical Center [74]. These data indicate that IHP for the treatment of non-resectable colorectal liver metastases can result in a considerable survival benefit. IHP with melphalan has been mainly applied for the treatment of colorectal liver metastases, but promising results have also been achieved using IHP for liver metastases from uveal melanoma [60, 70, 75].

References


