11. Locoregional techniques for liver-limited metastatic colorectal cancer

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Abstract. Local destruction techniques for colorectal liver metastases, particularly radiofrequency, have been incorporated into clinical practice in the past 5 years. Only 10% to 25% of patients with colorectal hepatic metastases have tumours that are potentially resectable. Local techniques represent a chance of treatment in conjunction with resection or as a standalone procedure.

It is difficult to compare ablation modalities. Results of studies examining these techniques are mostly restricted to reports of patient cases, which are often not presented in a standardised manner. Additionally, randomised controlled trials are rare.

Radiofrequency is the most extensively studied treatment modality, and response rates and survival after radiofrequency therapy have been established. Cryoablation and microwave ablation are employed in the same clinical setting as radiofrequency, but have less favorable safety profiles. Other local ablation techniques such as electrolysis, chemoembolization or high-intensity focused ultrasound are under development for colorectal liver metastases. Radioembolization and hepatic arterial
chemotherapy should be considered as therapeutic options for patients who are not candidates for resection or radiofrequency.

**Introduction**

Liver resection is the treatment of choice with the best chance for long-term cure in colorectal cancer patients with liver metastases[1-3]. However, most patients with liver-only metastases are not candidates for resection. The metastases may be inoperable due to a number of factors relating to the tumour distribution within the liver, the size of the tumour(s), and the presence of co-morbidities that preclude major surgery[4]. Novel approaches such as neoadjuvant chemotherapy, preoperative portal vein embolization, and two-stage hepatectomy have been used, but still not all metastases are safely resectable.

Over the past decade, a number of novel, less invasive methods of ablation have been developed. In patients requiring extensive liver resection, ablative techniques allow parenchyma-sparing treatment of hepatic metastases. In addition, some patients are not candidates for surgery owing to the presence of co-morbidities. In these patients, percutaneous ablation allows local treatment with lower morbidity and mortality. Therefore, this approach could increase the number of patients who are candidates for treatment. Ablative techniques may be considered alone or in conjunction with resection.

Several of these techniques have been developed specifically to treat unresectable liver metastases by inducing in situ coagulative necrosis. These techniques can be usefully divided into categories depending on their method of energy delivery or their mode of action.

The purpose of this chapter is to review the effectiveness of radiofrequency, cryoablation, microwave ablation, radioembolization, hepatic arterial chemotherapy, and other ablation techniques in the treatment of colorectal liver metastases.

1. **Radiofrequency**

   **Mechanism of action**

   Radiofrequency (RF) ablation induces a thermal injury to the tumour through electromagnetic energy deposition. The term radiofrequency does not refer to the emitted wave but to an alternating electric current that oscillates in the range of high frequency (200–1,200 kHz). The patient becomes a part of an electric circuit that includes a generator, grounding pads attached to the skin of the patient (usually on the thighs), and an electrode needle inserted into the tumour. When the generator is switched on, an alternating electric
field is created within the tissue of the patient. The ions in the tissue that surrounds the electrode experience an agitation following the changes in direction of alternating electric current. This ionic agitation creates friction within the surrounding tissue and releases heat around the electrode[5].

The thermal damage caused by radiofrequency is dependent on both the tissue temperature achieved and the duration of the heating. Heating of tissue at 50–55°C for 4–6 min produces irreversible cellular damage. At temperatures between 60°C and 100°C, tissue immediately coagulates, causing irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100–110°C, tissue vaporises and carbonises[5].

To ensure destruction of the tumour it is necessary to subject the entire tumour to cytotoxic temperatures for a certain period of time. A minimum may be to maintain a 50–100°C temperature throughout the entire tumour for at least 6 min. In fact, given the relatively slow thermal conduction from the electrode through the tissues, usually the duration of application is maintained during a minimum of 12–30 min, depending of the size of the tumour being treated[5].

The goal of the procedure is to create a necrotic region that includes the tumour and a safety margin surrounding the target. Most authors recommend a safety margin of 1 cm beyond the boundaries of the tumour[5]. However, this is a controversial issue.

Radiofrequency ablation is usually performed under intravenous sedation or, alternatively, general anaesthesia. The procedure may be performed

![Figure 1a. Liver sonogram with a focal hyperechoic lesion (arrow) in a patient with a history of a surgically removed colon cancer. A liver metastasis was demonstrated in the biopsy.](image)
Figure 1b. Radiofrequency ablation of the lesion. Using sonographic guidance, an electrode (arrowheads) has been percutaneously inserted through the liver into the lesion. Some minutes after starting the ablation, echogenic gas bubbles progressively appear around the tip of the electrode (arrows) as the ablation of the tumour progresses.

percutaneously, laparoscopically, or at open surgery. When a percutaneous approach is used, guidance of the placement of the electrode is more frequently performed with ultrasound (Figures 1a and 1b), and CT, but it can be performed using MRI as well[5].

Limits

The main problems with radiofrequency ablation are the relatively slow thermal conduction from the electrode surface through the tissues and the need to avoid carbonisation and vaporisation around the tip of the electrode due to excessive heating. Both carbonised tissue and vapour act as insulators, blocking the transmission of the electric current.

Two strategies have been used to increase the volume of ablation: to prevent overheating of the surrounding tissue, and to increase the number of active heads for treatment. The results are different kinds of electrodes:

- Internally cooled electrodes: the tip of the electrode is cooled by an inner circuit of circulating fluid to minimise carbonisation around the needle tip. In this way, the transmission of the electric current is not blocked, and a larger volume of tissue can be ablated.
- Multiple electrodes: several electrodes (usually up to three) work simultaneously to increase the total volume of ablation.
- Multitined expandable electrodes: these electrodes have several prongs that are deployed once the tip of the needle is in the tumour. The ablation volumes of each of these prongs combine to produce a larger total ablation volume. Some of these modified electrodes can ablate an area over 7 cm in diameter.
- Multitined perfused electrode: in this kind of electrode, a small volume of a saline solution is continuously injected through the tip into the surrounding tissues during the ablation. This fluid increases the conductivity of the treated tissue, allowing the radiofrequency current to penetrate further into the tissue, increasing tissue heating and necrosis.

Inadequate coagulation can also be due to the cooling effect of blood flow that can reduce the extent of thermal damage (the “heat sink effect”). Several strategies for reducing blood flow during ablation therapy have been proposed:
- Pringle manoeuvre (at open laparotomy and at laparoscopy).
- Embolization of the tumour-feeding artery.
- Combining thermal ablation with chemoembolization or transarterial administration of drug-eluting beads[5].

Experimental studies suggest that adjuvant chemotherapy may also increase the ablation volume. In an experiment in two animal models, Ahmed et al. found that RF ablation followed by IV liposomal doxorubicin resulted in a larger diameter of tumour necrosis than RF or doxorubicin alone. Combined therapy, as compared with liposomal doxorubicin therapy alone, was also associated with increased doxorubicin accumulation in the target organs[6].

When performing radiofrequency ablation in the liver, achieving a safety margin is more critical when treating liver metastases than when treating a primary tumour because metastases are usually surrounded by healthy liver parenchyma, throughout which the heat disperses easily. In the treatment of the hepatocellular carcinoma, the surrounding tissue is usually cirrhotic liver, which transmits heat poorly. So, the surrounding tissue concentrates the heat (the “oven effect”), potentiating the effect of the radiofrequency. Thus, the possibility of an incomplete treatment is higher in metastases than in hepatocellular carcinoma.

Results

Several studies have been published on the effectiveness of radiofrequency ablation in colorectal metastases to the liver (Figures 2a and 2b).
Figure 2a. One month after radiofrequency, a CT shows an area of non-enhancement (arrows) in the treated lesion. No signs of residual tumour are observed.

Figure 2b. On 2-year follow-up MRI after radiofrequency, the residual lesion has decreased in size and no signs of recurrence are observed.
It is important to specify that all of these studies have been carried out in the subset of patients not eligible for surgical resection and thus, the results should not be compared to results achieved with surgical resection.

There is a great deal of variability in the reported 5-year patient survival rate (14% to 55%) and local tumour recurrence rate (3.6% to 60%) in colorectal metastases treated with radiofrequency ablation. The variability of these rates can be attributed to increased experience with the technique as it becomes more widely used, and to differences in tumour selection criteria. The highest ablation success rates are achieved in patients with solitary metastases or with a small number of tumours, each tumour measuring less than 3 cm in diameter[5, 7-15].

Several studies with a large number of patients are listed in the Table 1.

In a recent study published by Otto et al. in two groups of patients with colorectal hepatic metastases amenable to surgery, patients treated with radiofrequency ablation as a primary option showed a higher frequency

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Access</th>
<th>3-year survival</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lencioni[10]</td>
<td>423</td>
<td>Percutaneous</td>
<td>47%</td>
<td>24%</td>
</tr>
<tr>
<td>Gillams[11]</td>
<td>309</td>
<td>Percutaneous</td>
<td>34%</td>
<td>24%</td>
</tr>
<tr>
<td>Siperstein[12]</td>
<td>234</td>
<td>Laparoscopic</td>
<td>20%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Solbiati[13]</td>
<td>117</td>
<td>Percutaneous</td>
<td>46%</td>
<td>36%</td>
</tr>
<tr>
<td>Veltri[14]</td>
<td>122</td>
<td>Percutaneous, Open</td>
<td></td>
<td>22%</td>
</tr>
<tr>
<td>Machi[15]</td>
<td>100</td>
<td>Percutaneous, Open, Laparoscopic</td>
<td>42%</td>
<td>31%</td>
</tr>
<tr>
<td>Sorensen[16]</td>
<td>100</td>
<td>Percutaneous, Open</td>
<td>64%</td>
<td>44%</td>
</tr>
<tr>
<td>Chen[17]</td>
<td>96</td>
<td>Percutaneous</td>
<td>25.1%</td>
<td></td>
</tr>
<tr>
<td>Amersi[18]</td>
<td>74</td>
<td>Percutaneous, Laparoscopic</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Jackobs[19]</td>
<td>68</td>
<td>Percutaneous</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Hildebrand[20]</td>
<td>56</td>
<td>Percutaneous, Open, Laparoscopic</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>
of local recurrence (32% vs. 4%) and a shorter time to progression (203 vs. 416 days), as compared to patients treated initially by surgery. However, after primary treatment, RF ablation patients and surgery patients were amenable to repeated RF ablation or repeated surgery, resulting in identical rates of disease-free and 3-year overall survival in both treatment groups (67% and 60%, respectively)[21].

Complications

Complication rate is proportional to the volume of tissue treated and increases in open radiofrequency ablation. Complication rates ranged between 13–27% after open treatment and 1.8–13% in percutaneous radiofrequency ablation. The incidence of major complications is 3.5–13% after open technique and 1.8–13% for percutaneous treatment. The published mortality rates in radiofrequency ablation for colorectal metastases have been 0–3.7% for open ablation and 0–0.5% after percutaneous treatment[5, 7-20].

Complications of radiofrequency ablation are similar for all ablative techniques and can be divided into two categories:

a. Related to the placement of the electrode

- Bleeding

The risk for bleeding is relatively low and depends on tumour location, vascularity of the tumour, and the presence of underlying liver disease. Given the relatively large bore of the electrodes used and the multiple insertions sometimes required, it is absolutely necessary to check for an appropriate coagulation status before performing the procedure[5, 9, 22].

- Infection

Hepatic abscess and sepsis are known complications of radiofrequency ablations. Radiofrequency ablation is a surgical procedure, so a strict adherence to sterile technique is compulsory to minimise the risk of infection. Diabetes and the presence of a bilioenteric anastomosis also increase the risk of sepsis after ablation[9, 22].

Non-specific fever after the ablation (“post-ablation syndrome”) is not uncommon but it is usually low-grade. When fever persists after 2–3 weeks, infection should be suspected[7, 22].
- **Tumour seeding**

  Track seeding has been reported as a late and infrequent complication (0.5%). Superficial location is one factor that increases the risk of seeding. To minimise this complication, it is important to meticulously ensure optimal positioning on the first pass to avoid repeated entries into the tumour with the electrode. Also, heating the electrode as it is withdrawn after the ablation (“hot withdrawal”) helps to destroy any tumour cells remaining in the track[5, 7, 9, 22].

- **Pneumothorax**

  Pneumothorax can occur when the electrode crosses the pleural recess. This occurs more frequently when CT is used as the method of guidance given that, ideally, an axial plane should be used to monitor the path of the electrode[5, 7-9, 22].

**b. Related to thermal therapy**

- **Thermal damage to adjacent structures**

  The heat delivered can affect not only the intended target but it can also damage adjacent structures. The bile ducts are the most frequently damaged structures and bile duct strictures can occasionally be observed after the procedure. Also, the gallbladder and bowel are very sensitive to thermal insults, and cholecystitis and bowel perforation may appear when the tumour is located near these structures. Perforation occurs more frequently in the colon[5, 7, 9, 22].

  Perforation of the gastrointestinal wall is probably the most feared complication and can be fatal. A history of previous abdominal surgery in the region adjacent to the tumour and chronic cholecystitis are both associated with an increased risk of perforation. It is possible that heat is more easily transmitted through the scars and adhesions caused by previous interventions. The colon, which is fixed to retroperitoneum, is the part of the gastrointestinal system most frequently damaged during ablations, due to its lack of mobility[22].

  Careful planning before ablation is essential to avoid damaging these structures. One option to avoid thermal damage and to protect sensitive structures is to percutaneously inject air or fluid between the treatment area and the potentially damaged structure in order to create a protective gap. Another possibility is to use a laparoscopic or an open approach. A thermocouple, placed next to the structure that should be protected, can also be used to monitor the temperature and warn the surgeon when a dangerous level is reached.
- Hepatic failure

Ablation of a large volume of tissue as a result of treatment of multiple lesions or aggressive creation of a wide ablative margin may be harmful. It may damage hepatic structures and may preserve too little normal tissue to permit adequate hepatic function, leading to a hepatic failure, especially in patients with previous hepatic surgery[22].

- Grounding pad burns

Large grounding pads are used to disperse the electric current and close the electric circuit in the patient. These pads receive the same energy loads and produce the same amount of heat as the electrode, but over a larger surface. An inadequate placement of these pads may concentrate the heat in a small area causing second- and third-degree skin burns. Care should be taken to ensure that the grounding pads are placed equidistant from the electrode[22]. This is currently a rare complication which usually appears only in the initial phases of the learning curve.

- Interferences with pacemaker and cardioverters

Despite some concerns regarding the possible risk associated with performing radiofrequency ablation in patients with a pacemaker, no problems have been reported in these cases. However, some concern still exists regarding patients with an implantable cardioverter-defibrillator. In these patients, it may be advisable to inactivate the ventricular arrhythmia sensor if radiofrequency ablation is to be performed[5, 7-9, 22].

- Pleural effusion

This occurs most frequently when treating lesions located near the diaphragm. It is the consequence of the thermal damage to the diaphragm and the adjacent pleura[7].

2. Cryoablation

Mechanism of action

The physiological basis of cryotherapy is the rapid formation of intracellular ice crystals, resulting in direct cell damage. In addition, hypoxia secondary to the disruption of the surrounding microvascular structures induces cell destruction. Cryoablation uses repetitive freezing and thawing of
tissue to produce necrosis and irreversible tissue destruction. Both liquid nitrogen and argon gas can be used as coolants and are capable of producing temperatures as low as -40°C. Cell destruction is directly proportional to the rapidity and duration of freezing and the rate of thawing. Cryoablation of 1 cm of normal liver parenchyma around the treatment area is recommended to obtain complete ablation. Cryoablation is easy to monitor with ultrasound, which allows for accurate, real-time assessment during treatment.

Limits

The local recurrence rate is higher for metastases adjacent to a major hepatic vessel. Even though technically this area is not a heat sink, it is thought that inflowing warm blood has a protective effect and prevents adequate freezing[4]. Larger lesions may be difficult to treat because large volumes of normal liver parenchyma may have to be subjected to lethal temperatures and conduction of cold is substantially reduced as the distance from the probe increases.

Results

The rate of local recurrence varies from 9% to 44% in different reports[23-25]. These studies are difficult to compare due to the heterogeneity of the patients (number and size of lesions, local and systemic treatments received). One of the few trials comparing RF and cryotherapy found a 12%

Table 2. Results of cryoablation studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Recurrence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-year</td>
<td>5-year</td>
</tr>
<tr>
<td>Weaver[27]</td>
<td>38%</td>
<td>40%</td>
</tr>
<tr>
<td>Seifert and Morris[28]</td>
<td>33%</td>
<td>8%</td>
</tr>
<tr>
<td>Sheen[29]</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Yan[30]</td>
<td></td>
<td>41%</td>
</tr>
<tr>
<td>Kerkar[31]</td>
<td>15%</td>
<td>48%</td>
</tr>
<tr>
<td>Seifert[32]</td>
<td>24%</td>
<td>42%</td>
</tr>
<tr>
<td>Joosten[33]</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>Brooks[34]</td>
<td></td>
<td>43%</td>
</tr>
<tr>
<td>Yan[35]</td>
<td>39%</td>
<td>43%</td>
</tr>
<tr>
<td>Niu[36]</td>
<td>78%</td>
<td>43%</td>
</tr>
</tbody>
</table>
local recurrence rate with cryoablation and 14% with RF (no significant difference)[26].

Survival rates are difficult to establish because reports of 3- and 5-year survival rates are uncommon in the literature, and cryotherapy is frequently combined with other treatments. A summary of the results of cryoablation studies is presented in Table 2.

Complications

The most serious complication of cryotherapy is the post-treatment syndrome referred to as cryoshock. This is a systemic response that consists of coagulopathy, thrombocytopenia, pleural effusions, an acute respiratory distress syndrome-like illness, and myoglobinuria. Reports in the literature suggest a mortality rate of 0% to 8%, although it may be responsible for 18% of perioperative deaths[37]. The cryoshock phenomenon correlates with the duration and volume of freezing and with hepatocellular injury[38].

Other major complications such as hemorrhage, subphrenic abscesses, biliomas and biliary fistulae frequently occurred in each of the studies, and there is a direct relationship between the volume of liver ablated and the incidence of complications. A few retrospective studies comparing radiofrequency with cryoablation found higher rates of complications, blood loss, and length of stay in patients treated with cryoablation[4, 26].

3. Microwave ablation

Mechanism of action

Microwaves with frequencies in the range of 900–2,450 MHz induce tumour destruction. Within this electromagnetic field, polar molecules align themselves in the direction of the current. As the direction changes constantly, this continuous realignment causes a heating effect, and electromagnetic energy induces cell death by coagulative necrosis. This procedure may be performed percutaneously, laparoscopically, or during open surgery.

Limits

One of the main limitations of this technique is the difficulty of creating consistent ablation zones larger than 3 cm.

Microwave ablation has principally been used in hepatocellular carcinoma but is also used in some colorectal liver metastases. In colorectal liver
metastases, its use is still in development, and few studies have been published.

**Results**

Published studies so far are limited, with a small number of patients and a lack of long-term comparative survival data. Primary and secondary tumours treated with microwave ablation have a local recurrence rate of 6% in reference centres, and select patients have a 3-year overall survival of 40%. The main studies are shown in Table 3.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Recurrence</th>
<th>3-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibata[39]</td>
<td>14</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Tanaka[40]</td>
<td>16</td>
<td>22%</td>
<td>39%</td>
</tr>
<tr>
<td>Bhardwaj[41]</td>
<td>31</td>
<td>6%</td>
<td>40%</td>
</tr>
</tbody>
</table>

**Complications**

A high rate of complications (as high as 20.6%) has been reported in patients treated for colorectal metastases[42]. These complications are bleeding, bilioma formation, tumour dissemination, portal vein thrombosis, or post-ablation pneumothorax. The incidence of complication increases when the tumour size exceeds 4 cm [42].

**4. Radioembolization**

**Mechanism of action**

Radioembolization or selective internal radiation therapy with microspheres loaded with the radionuclide yttrium-90 ($^{90}$Y) enables multiple hepatic metastases to be targeted in a single procedure. The $^{90}$Y-resin microspheres lodge within the malignant microvasculature, where they deliver high, localised therapeutic doses of β-radiation to the tumour over approximately 14 days, while maintaining the radiation exposure of normal liver within tolerable levels[43]. In a study that measured tumour dosimetry in the human liver following hepatic yttrium-90 microsphere therapy, the authors found that the average level of radiation within the tumour periphery ranged from 200 Gy to 600 Gy, while in the normal liver parenchyma the average level was 8.9 Gy[44].
Limits

A simulation of the treatment is first performed by injecting tracer doses of technetium-99m-labelled macroaggregated albumin ($^{99}$Tc-MAA) intra-arterially. The distribution of the $^{99}$Tc-MAA is accepted as an accurate representation of the distribution of the microspheres. The tracer uptake in the body is then quantified. If the lungs absorb >20% of the injected dose, treatment is contraindicated. During the interventional procedure, all collateral vessels that can transport microspheres from the targeted liver vasculature to extrahepatic organs are occluded by embolization to prevent systemic deposition of $^{90}$Y-microspheres. If there is abdominal $^{99}$Tc-MAA deposition outside of the liver, it is recommended to repeat the angiogram and the prophylactic embolization procedure, and to re-inject the $^{99}$Tc-MAA. Additionally, the presence of main portal vein thrombosis or pulmonary arterial thrombosis is a contraindication for the treatment[45, 46].

Results

This procedure is being used increasingly to manage liver tumours of various histological origins. In some studies of colorectal liver metastases, $^{90}$Y-microspheres have been combined with systemic chemotherapy or hepatic arterial infusion, with an encouraging median survival and response rate[47, 48]. Very few randomised controlled trials of radioembolization in colorectal liver metastases have been published. In phase I and II studies, radioembolization significantly decreased the average tumour size and increased the time to progression. The main studies related to radioembolization are summarised in Table 4. In a phase III randomised study, patients received hepatic artery chemotherapy with or without a single injection of $^{90}$Y-resin microspheres. Patients receiving radioembolization had a significantly higher tumour response rate and a lower rate of hepatic progression compared with those receiving artery chemotherapy alone[49]. Another phase III trial assessed the efficacy of $^{90}$Y-microspheres in chemotherapy-refractory liver-limited colorectal cancer metastases[45]. The authors compared protracted fluorouracil intravenous infusion with or without radioembolization. The combined treatment improved the time to progression compared with fluorouracil alone.

Therefore, radioembolization with $^{90}$Y-resin microspheres should be considered a valid therapeutic option for patients with liver-limited metastatic colon cancer, but questions remain regarding its timing and optimal combination schedule. Potentially, more effective chemotherapeutics combined with targeted therapies have been introduced into the clinic, and the clinical value of $^{90}$Y-resin microspheres when compared to these novel treatments warrants confirmation and validation.
<table>
<thead>
<tr>
<th>Study</th>
<th>Phase (no. of patients)</th>
<th>Schedule</th>
<th>Response rate</th>
<th>Time to progression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma[50]</td>
<td>I (n=20)</td>
<td>FOLFOX + radioembolization</td>
<td>90%</td>
<td>12.3</td>
</tr>
<tr>
<td>Van Hazel[51]</td>
<td>I (n=25)</td>
<td>Irinotecan + radioembolization</td>
<td>48%</td>
<td>6.6</td>
</tr>
<tr>
<td>Cosimelli[52]</td>
<td>II (n=50)</td>
<td>Radioembolization</td>
<td>24%</td>
<td>OS: 12.6</td>
</tr>
<tr>
<td>Van Hazel[53]</td>
<td>Randomised II (n=21)</td>
<td>5FU/LV</td>
<td>0%</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5FU/LV + radioembolization</td>
<td>72%*</td>
<td>3.6 *</td>
</tr>
<tr>
<td>Gray[49]</td>
<td>III (n=74)</td>
<td>HAC</td>
<td>17.6%</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAC + radioembolization</td>
<td>44%*</td>
<td>15.9*</td>
</tr>
<tr>
<td>Hendlisz[45]</td>
<td>III (n=44)</td>
<td>5FU</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5FU + radioembolization</td>
<td>4.5*</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; HAC, hepatic artery chemotherapy
*Statistically significant difference
Complications

Radioembolization can lead to fatigue, vomiting, anorexia, fever, abdominal discomfort, and cachexia. Hepatic toxicity can be assessed by changes in the levels of liver enzymes and metabolites; these changes can be severe and can lead to significant morbidity and mortality. Hepatic toxicity rates following radioembolization are between 15% and 20%. Various factors such as the presence of altered hepatic function at baseline, age, and radiation distribution may predispose patients to the hepatotoxic effects of radioembolization. Radiation-induced liver disease (RILD) has been observed in 4% of patients. Less than 2% of patients develop severe biliary toxicity, and cholangitis has also been reported following radioembolization. Portal hypertension due to post-embolization fibrosis is possible, but the clinically significant occurrence of portal hypertension is low[45, 46].

The inadvertent spread of microspheres to the gastrointestinal tract is responsible for potentially severe complications such as ulceration. Radiation pneumonitis has been observed when the lung shunt fraction is greater than 13%[45, 46].

Adverse events with radioembolization are mainly low and manageable. Only a limited number of patients develop gastrointestinal ulceration, bleeding or microsphere embolization in other organs.

5. Hepatic arterial infusion (HAI) of chemotherapy

Mechanism of action

The rationale for hepatic arterial infusion (HAI) is that hepatic metastases are fed by the hepatic artery, while the normal liver parenchyma is fed mostly by the portal vein. Infusing cytotoxic agents directly into the hepatic artery leads to prolonged elevated levels of the drug within tumour cells, with relative sparing of normal liver parenchyma. Agents with high hepatic extraction rates are particularly attractive for HAI. Floxuridine (FUDR: 5-fluoro-2’-deoxyuridine) has a 95% hepatic extraction rate when given via HAI. Phase I/II trials are ongoing to assess the efficacy of other cytotoxic agents such as oxaliplatin, cisplatin, mitomycin-C and irinotecan using HAI[54].

Limits

All patients should have a nuclear medicine macro-aggregated albumin scan to assess whether the perfusion is contained to the liver or if there is extrahepatic perfusion. If there is misperfusion to the stomach or duodenum,
ulceration or diarrhea can result. A subcutaneous pump connected to an arterial catheter must be surgically implanted.

Results

Early clinical series using FUDR delivered as continuous HAI produced encouraging results. In subsequent years, prospective randomised phase III trials were published. In the 1990s, seven studies compared HAI FUDR with systemic FUDR or 5-FU ± LV. The response rates were high, but benefit in overall survival was found only in two studies. Two meta-analyses included these trials and showed an increase in response and a survival advantage[55, 56]. However, two more recent European trials did not show any increase in survival [57, 58]. Some drawbacks to these studies have been discussed: 1) the number of patients was small; 2) a crossover design was allowed; 3) patients with extra-hepatic disease were included; and 4) many who were assigned to the HAI arms did not receive treatment. To avoid these biases, the CALGB-9481 study was initiated[59]. This study compared HAI FUDR against systemic 5-fluorouracil/lecovorin. The HAI group showed a significant increase in overall survival (24.4 months vs. 20 months; \( p = 0.0034 \)), and the time to progression was superior in the HAI arm (9.8 months vs. 7.3 months; \( p = 0.12 \)). Finally, a meta-analysis pooling individual patient data from 10 studies was published[60]. The response rate was 42.9% vs. 18.4% for HAI vs. systemic treatment, and the median overall survival was 15.9 months vs. 12.4 months for the HAI and systemic groups, respectively (HR = 0.9; \( p = 0.24 \)). Despite a number of randomised clinical trials, the therapeutic impact of fluoropyrimidine-based HAI is still a matter of debate. HAI provides a tumour response advantage when compared with fluoropyrimidine-based systemic infusion; however, modern chemotherapy schedules can obtain tumour response rates similar to or even higher than those observed with HAI. Furthermore, an advantage in overall survival needs to be clarified.

HAI added to systemic chemotherapy might control hepatic disease and prevent extra-hepatic metastases. New HAI protocols that use concomitant or alternating modern systemic chemotherapy have increased response rates, leading to increased resectability of liver metastases. However, published series are short, retrospective, or are early phase trials. Further trials comparing HAI plus systemic chemotherapy vs. systemic chemotherapy alone are needed to determine the relative merits of each.

Complications

Biliary sclerosis determines the dose-limiting toxicity because the hepatic artery supplies blood to the bile ducts. The addition of dexamethasone to FUDR reduces biliary toxicity.
Early complications are more likely to involve misperfusion of the liver. Other early complications are pocket infections or hematomas, incomplete perfusions, and thrombosis. Late complications include occlusions, dislodgement, catheter occlusions, or arterial thromboses. Very rarely, the catheter can come out of the artery and abdominal blood loss can occur. Hepatotoxicity depends on the drugs used and the duration of treatment[54].

6. Other locoregional ablation techniques

Other techniques, such as electrolysis, chemoembolization, and high-intensity focused ultrasound, have been developed to treat local liver tumours.

Electrolysis uses direct current passed between two electrodes. The negatively and positively charged ions in the tissue are attracted to the anode and cathode, respectively. This results in tissue destruction around the anode and cathode. The principal disadvantage of this technique compared with microwave and radiofrequency ablation is the relatively long period of time required to create similarly sized lesions; however, its safety profile is acceptable. Long-term survival data are awaited, and if these data are encouraging, electrolysis must be further refined to induce lesions more quickly[61].

Hepatic arterial embolization with the injection of vasoocclusive particles into the hepatic artery can occlude the blood supply to the tumour metastases. Chemoembolization involves local entrapment of the drug in an appropriate vehicle (the embolic agent), thus providing prolonged exposure of tumour to the drug with minimal systemic drug circulation. This strategy has been employed using doxorubicin, mitomycin-C, and cisplatin in the embolic agent lipiodol, and, more recently, with embolic doxorubicin as a drug-eluting bead. This later strategy has demonstrated response rates in hepatocellular carcinoma but is rarely used to treat liver metastases from colorectal cancer as a single entity[61].

High-intensity focused ultrasound (HIFU) ablation for liver tumours is an extracorporeal non-invasive treatment method using focused ultrasound beams that can cause complete coagulative necrosis of target lesions. For treating liver metastases from colon cancer, HIFU seems to be safe, but its efficacy is questionable. Therefore, further research is warranted[62].

Conclusion

Although surgery is currently the only potentially curative treatment for liver metastases from CRC, however, fewer than 25% of cases are
candidates for curative resection. A number of other locoregional therapies, such as radiofrequency or microwave ablation, cryotherapy, and chemotherapy, may be offered to patients with unresectable but isolated liver metastases.

RF is the ablation procedure most used and it may be performed intraoperatively, laparoscopically, or percutaneously. The percutaneous approach is associated with the least procedural risk and may be performed under local anesthesia. This approach should be considered a safe, effective and potentially curative option as a primary treatment for patients with unresectable liver tumours or conditions that prohibit general anesthesia or abdominal surgery. Its long-term results are comparable with those of investigations using surgical resection. The factors such as lesion size, the number of lesions and location determine its success.

Cryoablation and microwave ablation are employed in the same clinical setting but with less favorable safety profiles. Other local ablation techniques such as electrolysis, chemoembolization or high-intensity focused ultrasound are under development for CRC liver metastases. Finally, radioembolization and hepatic arterial chemotherapy should be considered as therapeutic options for patients who are not candidates for resection or radiofrequency.

References

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