

# CHAPTER 21 MANAGEMENT OF LIVER AND OTHER DISTANT METASTASES

## 21.1 Liver metastases

Fifty per cent of patients with Colorectal Cancer will develop liver metastases within five years. In 20–40% of cases, this will be the only (or first) site of failure. Management of liver metastases can involve one or more of the following treatment modalities:

- surgical resection
- image controlled destruction
- hepatic arterial infusion
- palliative chemotherapy (see Chapter 20)
- palliative radiation therapy.

### 21.1.1 Surgical resection

Approximately 50% of patients who undergo resection for Colorectal Cancer will develop recurrent disease within 5 years. The liver is the major site of recurrence and the primary determinant of patient survival. Systematic attempts to resect colorectal liver metastasis were commenced some 40 years ago<sup>1,2</sup> and subsequently became more widely accepted. A large number of reports showed that resection for colorectal liver metastasis was safe and potentially curative.<sup>3–6</sup> It is well established that isolated liver metastasis can occur without growth elsewhere and that surgical excision of liver tumours could be performed with low morbidity and mortality.<sup>7</sup>

There have been no controlled studies of surgery versus no treatment or chemotherapy for resectable disease. The studies of the natural history of liver metastases have been quite rightly criticised in regard to the lack of data on extent of liver involvement and comparison with historical controls from an era when clinical examination was the only method of determining metastatic disease to the liver. However, some authors have attempted to assess the natural history of potentially resectable disease that was not resected because of the therapeutic approach at that time. Wood<sup>8</sup> reported on 25 of 113 patients who were thought, retrospectively, to have potentially resectable disease. The survival at one, three and five years was 46%, 12% and 3% respectively. Wagner's study<sup>9</sup> showed three- and five-year survival for untreated, resectable disease was 14% and 2% respectively. Scheele<sup>10</sup> reviewed 62 patients with resectable disease that were not treated and found a three- and five-year survival of 10% and 0% respectively.

The data from these studies indicated that solitary or unilobar disease appeared to have a better prognosis, but had a uniformly bad prognosis when not treated, with 5-year survival consistently below 3%. However, liver metastases are common and most patients will not be helped by resection. As stated by Adson,<sup>11</sup> 'There is a need to distinguish between the limited influence of resection on a total population and the benefits available to a well-defined subgroup that can be treated well'.

The biology of the disease will determine the long-term outcome and better imaging modalities have resulted in better selection of patients to be offered resection. Retrospective studies have attempted to define good and bad prognostic indicators for long-term outcome. There have been conflicting statements regarding age<sup>12</sup> and sex as significant risk factors and similar results have been reported with synchronous or metachronous liver metastases.<sup>3–6,13–15</sup> In addition, bilobar liver metastases do not appear to influence outcome, provided it is resectable.<sup>3,5,6,13</sup> The characteristics of metastatic disease that correlate with poor outcome appear to be more than three metastases,<sup>15,16</sup> increasing tumour size<sup>15</sup> and an involved surgical margin.<sup>5,15</sup> However, recent reports have questioned the upper limit of three

metastases and have shown equivalent results with four or more metastases, provided complete resection with a tumour-free margin is achieved.<sup>17,18</sup> Several studies have suggested that the level of preoperative CEA may correlate with outcome,<sup>18-21</sup> although the critical level has variously been set from 30–200 ug/ml. In multivariate analyses, the most consistent predictors of long-term outcome have been stage of the primary tumour, total of liver involvement and complete resection.<sup>7</sup> However, Hughes<sup>22</sup> and Fong<sup>21</sup> have shown that a number of patients with poor prognostic indicators survived 5 years after liver resection and concluded that each case must be individually assessed on its merits.

In an endeavour to aid the appropriate selection of patients who may benefit from resection for metastatic Colorectal Cancer, Fong and his colleagues,<sup>21</sup> by analysing clinical, pathologic and outcome data on 1001 patients, established a clinical risk score for tumour recurrence. Five clinical criteria available before liver resection — nodal status of the primary; disease-free interval from the primary to discovery of the liver metastases of <12 months; number of tumours >1; preoperative CEA level of >200 ng/ml; and size of the largest tumour >5 cm — were chosen as criteria for a clinical risk score. Each criterion was assigned one point and the total score was compared with the clinical outcome of each patient. The total score was found to be highly predictive of long-term outcome. Such a clinical score may help the surgeon and the patient to be better equipped to make a rational decision about the individual patient.

There are a number of reports of repeat hepatic resection for recurrent colorectal liver metastases with results comparable to those after initial resection.<sup>18,20,21,23-26</sup> What has become evident is that some of the improvement in overall survival has been a result of repeat resection in selected patients, and this may also be applicable with methods using physical ablation.

Most series of liver resection for colorectal metastases have reported five-year survival around 25-35%, with a median survival of greater than two years. While there are no concurrent control groups of resectable but untreated patients, it would be difficult to run a controlled trial with a no-treatment arm. It is imperative that there be a low morbidity and mortality. Mortality of liver resection in most major hepatobiliary units in Australia is less than 2%. The evidence available from the many studies worldwide would support the proposition that liver resection is the only chance of cure in a selected group of patients who fit defined criteria as outlined.

### **21.1.2 Adjuvant chemotherapy following surgical resection**

Four recent randomised studies<sup>27-30</sup> have attempted to define the benefit of adjuvant flouoropyrimidine chemotherapy, delivered via a hepatic artery catheter and/or intravenously, following resection of hepatic metastases. A consistent trend toward improved survival outcomes has been demonstrated in each of these studies.

In one study<sup>27</sup> that compared intra-arterial hepatic chemotherapy plus systemic chemotherapy versus systemic chemotherapy alone, a statistically significant survival advantage and reduction of recurrence within the liver was found with combined therapy, but at a cost of higher side effects. Another trial<sup>28</sup> of hepatic arterial infusion with continuous intravenous 5-FU infusion compared to observation found an increased time to recurrence and fewer liver relapses, but median survival was not statistically significant. A Cochrane review of all trials that have randomised patients following liver resection to hepatic artery chemotherapy or any alternative treatment concluded that recurrence in the remaining liver happened less in the hepatic artery chemotherapy group, but that this did not lead to an improvement in overall survival.<sup>31</sup>

The two trials<sup>29,30</sup> that compared systemic bolus 5-FU plus leucovorin to observation alone; each showed only a trend to benefit of chemotherapy. Each study was only powered to show a very large difference. On the basis of these studies it is reasonable to offer adjuvant chemotherapy following surgical resection of liver metastases, but it cannot be considered standard treatment.

### 21.1.3 Imaging controlled destruction

Local ablative therapies for the treatment of colorectal hepatic metastases have been the focus of much recent research, with most interest being shown in radiofrequency (thermal) ablation (RFA or RFTA). This treatment involves percutaneous (or, less frequently, intraoperative) placement of a metallic probe into a hepatic lesion, using imaging guidance (usually ultrasound, occasionally CT or MRI). Radiofrequency energy passed through the probe causes local ionic excitation resulting in the lesion being ‘heated’ to a level where cell death occurs. The major technical issues are charring at the needle tip and incomplete treatment, based on the proximity of a lesion to vascular structures which act as a ‘heat sink’.<sup>32–34</sup> The procedure may be performed on an outpatient basis using local anaesthetic and intravenous sedation. Most patients can be treated in a single session. Complication rates are as follows: mortality 0.5%, major complications 2%, minor complications 6%.<sup>35,36</sup>

Patient eligibility varies between institutions and individuals. There are no accepted standardised criteria. In general, patients should not be surgical candidates (either because of anticipated technical resection difficulties, or comorbidities), have five or less lesions each less than 5 cm in diameter and be free of other distant metastases.<sup>33</sup> Lesion location may also play a part in selection. Those close to or abutting the gallbladder, hepatic flexure of the colon, diaphragm and hepatic hilum require great care in treatment to avoid heat-related damage and may result in patient exclusion.<sup>33</sup>

As with all relatively new treatment modalities, little robust data is available in the form of randomised controlled trials and long-term survival statistics. A single prospective randomised controlled trial comparing RFA with surgery for solitary colorectal metastasis has been published, demonstrating similar median and 3-year survival rates between the two treatment modalities.<sup>37</sup> The largest published series to date, of 117 patients with hepatic metastases from colorectal carcinoma, reported that technical success (no radiologically detectable tumour at 7–14 days after treatment) was achieved in 98% of patients.<sup>38</sup>

Many other local ablative techniques are under investigation.<sup>33,39–42</sup> These include laser-induced thermotherapy, microwave therapy and high-frequency targeted ultrasound. Cryoablation has been largely abandoned due to a higher rate of major complications than for RFA.

#### Should imaging controlled destruction be considered?

Guideline — Imaging controlled destruction	Level of evidence	Practice recommendation	Refs
Radiofrequency ablation is an alternative to surgery in selected cases.	II	Equivocal	37

## 21.2 Chemotherapy for patients with unresectable liver metastases

### 21.2.1 Hepatic arterial infusion

Hepatic arterial infusion (HAI) involves the administration of chemotherapy agents directly into the liver through a catheter surgically implanted into the hepatic artery.

Potential advantages of this approach include:

- liver metastases mainly derive their blood supply from the hepatic artery rather than the portal vein<sup>43</sup>
- a mean hepatic drug concentration approximately 15-fold higher than can be achieved with intravenous chemotherapy<sup>44</sup>

- almost all (94–99%) administered floxuridine, an effective drug for the treatment of Colorectal Cancer, is metabolised by the liver during first pass, which reduces systemic drug concentrations and resulting toxicity.<sup>45–47</sup> However, this also means the systemic concentration of FUDR is insufficient to treat any extrahepatic metastases.

Technical complications include an operative mortality below 1% in experienced hands, mechanical problems related to the catheter such as leakage, kinks, migration or breakage (5%), vascular complications from the catheter such as thrombosis or aneurism formation (5%), and problems associated with implantable pumps (8%).<sup>44–47</sup> Toxicities from intrahepatic chemotherapy include sclerosing cholangitis (10%), which is occasionally fatal, chemical gastritis (10%) and peptic ulceration (5%).<sup>45</sup>

### 21.2.2 Efficacy of hepatic arterial infusion

Pooled data from a meta-analysis of six of the seven randomised studies published between 1988 and 1993 confirmed the significantly higher response (41% compared to 14%) for HAI compared with intravenous 5-FU-based chemotherapy.<sup>48</sup> However, this analysis failed to demonstrate a significant survival benefit favouring HAI. In a recent study published by Lorenz et al,<sup>49</sup> 168 patients with unresectable liver metastases were randomised to receive intravenous 5-FU, HAI 5-FU or HAI FUDR. As expected, HAI chemotherapy (5-FU or FUDR) produced a higher response rate than intravenous 5-FU ( $p = <.05$ ), however treatment with HAI FUDR resulted in an increased number of patients developing extrahepatic metastases at six months ( $p = <.05$ ), and a trend toward increased early deaths and inferior overall survival. In a similar study by Kerr et al<sup>50</sup> comparing intravenous and HAI 5-FU, no differences in progression free or overall survival were demonstrated between the two.

### 21.2.3 Alternatives to hepatic arterial infusion

In patients with metastatic Colorectal Cancer, randomised studies of combination chemotherapy regimens that include 5-FU plus irinotecan or oxaliplatin have consistently produced response rates in the order of 40–50%, and median survivals approaching 18 months<sup>51–55</sup> (see Chapter 20). Patients with metastases confined to a single organ, such as the liver, will achieve a higher response rate than those with multiple sites of disease.<sup>51,52,54</sup> For patients with liver-only metastases, the combination of 5-FU plus oxaliplatin may be superior to 5-FU plus irinotecan, but this data is somewhat subjective at present.<sup>54–56</sup>

Giachetti et al<sup>56</sup> analysed a series of 151 patients with Colorectal Cancer metastases confined to the liver but considered unresectable due to large tumour size, more than four metastases, or ill-located metastases. All patients received treatment with infusional 5-FU, leucovorin and oxaliplatin. The overall response rate was 59%. Surgery with curative intent was attempted in 77 patients (51%), with complete resections being achieved in 58 patients (38%). Fifty per cent of the 77 operated patients were alive at five years of follow up.

No randomised studies comparing HAI with combination regimens have been or are likely to be performed. However, given the consistently impressive response rates and survival figures achieved with current combination chemotherapy regimens, and the inferior safety profile and minimal effect on subclinical extrahepatic metastases of HAI, HAI should not be considered standard therapy in this context.

### Should adjuvant chemotherapy be considered?

Guidelines — Chemotherapy for hepatic metastases	Level of evidence	Practice recommendation	Refs
Adjuvant chemotherapy should be considered following resection of liver metastases.	II	Equivocal	27–30

## Does combination systemic chemotherapy have any benefits?

Guidelines — Chemotherapy for hepatic metastases	Level of evidence	Practice recommendation	Refs
Combination systemic chemotherapy regimens that incorporate irinotecan or oxaliplatin have response rates, survival outcomes and safety profiles that appear superior to those achieved with hepatic artery infusion chemotherapy.	III	Recommend	48, 51–55

## When should surgical resection of unresectable liver metastases be considered?

Guidelines — Chemotherapy for hepatic metastases	Level of evidence	Practice recommendation	Refs
Patients with liver metastases that are initially considered unresectable and who are achieving a response to systemic chemotherapy should be reconsidered for surgical resection.	III-3	Recommend	56

### 21.2.4 Palliative chemotherapy

See Chapter 20.

### 21.2.5 Palliative radiation therapy

Palliative radiation therapy has been used for the management of symptomatic liver metastases for over 30 years. The most common symptoms that may result from liver metastases are pain, sweating, nausea and vomiting. Generally, radiation therapy to the liver results in low toxicity<sup>57,58</sup> and reasonable response rates of symptom relief.<sup>59</sup> Its popularity in recent times has been overshadowed by the development of newer systemic agents and the increasing use of interventional techniques. There has also been the misconception that radiation therapy to the liver results in radiation hepatitis. This is certainly not true provided that high doses are given to only part of the liver<sup>60</sup> or the whole liver dose is restricted to 30 Gy in 15 fractions<sup>61</sup> or 21 Gy in three fractions.<sup>62</sup> More recently, a prospective study in Australia and New Zealand has evaluated 10 Gy in two fractions given on consecutive days.<sup>63</sup> This study reported good relief of symptoms without adverse toxicity.

### 21.2.6 Treatment of peritoneal carcinomatosis

Peritoneal carcinomatosis from colorectal origin is a common condition facing many surgeons and medical oncologists. It has been estimated that up to 25% of patients die from peritoneal carcinomatosis, even when no other sites of metastases can be found.<sup>70</sup>

Traditional teaching states that once a Colorectal Cancer has disseminated intra-abdominally, no other surgery should be offered apart from resection of the primary tumour and systemic chemotherapy.

This philosophy has come about because of the generally poor prognosis of patients with peritoneal carcinomatosis, with most studies often quoting median survival of six months.

There was only one published randomised controlled trial comparing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy. With 50 patients in each arm, the median survival was 12.6 months in the systemic chemotherapy arm and 22.3 months in the surgery arm ( $p = 0.032$ ). The five-year survival rate was 20%. However, this trial was criticised

for using older generation systemic chemotherapy protocols.<sup>70</sup> A recent multi-institutional study with 506 patients from 28 institutions had an overall median survival of 19.2 months, with morbidity and mortality rates of 23% and 4% respectively.<sup>71</sup>

Critics of cytoreductive surgery with HIPEC have two main arguments. The first is that combination systemic chemotherapy using fluorouracil plus leucovorin, irinotecan and oxaliplatin in the treatment of advanced Colorectal Cancer can produce median survival rates of 20 months.<sup>72</sup> However, most patients had liver metastases without peritoneal carcinomatosis and better outcomes in this group of patients would be expected.

The second is the high operative mortality rate, with some centres reporting up to 8% 30-day mortality. This was the reported mortality rate during the early phase or 'learning curve' of cytoreductive surgery with HIPEC. The majority of the deaths were due to intraperitoneal chemotherapy complications during phase II trials. Most units are now reporting 30-day mortality rates of 4%, which is acceptable in major cancer surgery.<sup>73-76</sup>

### What is the role of cytoreductive surgery with hyperthermic intra-peritoneal chemotherapy?

Guidelines — Peritoneal carcinomatosis	Level of evidence	Practice recommendation	Refs
Cytoreductive surgery with or without chemotherapy should be performed on an appropriate randomised controlled trial.	II	Equivocal	70-82

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