Review

Surgical management of hepatic metastases from colorectal malignancies

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Summary

Liver metastasis represents the major cause of death of patients who have been treated for colorectal adenocarcinoma. Spontaneous survival rarely exceeds two years. Surgery can offer long-term survival and resection should be considered when liver metastases can be totally resected with clear margins and when there is no non-resectable extra-hepatic disease. The choice between anatomical or wedge resection depends on the number and the location of the metastases but does not influence survival. Clamping methods limit blood loss. Operative mortality is generally less than 5%. The five-year survival rate after surgical resection varies from 20% to 45% according to several prognostic factors. The longer survival is observed in patients with fewer than four lesions, with lesions smaller than 4 cm, without extra-hepatic disease, with lesions that appeared more than two years after the resection of a stage I or II colorectal cancer and whose CEA level is normal.

After resection, follow-up can detect hepatic recurrence that can be treated with repeat hepatectomy. The efficacy of systemic chemotherapy using new agents can increase the number of patients amenable to surgery. Regional therapies with cryotherapy or radiofrequency ablation can help to treat unresectable or non-totally resectable lesions and may improve survival. The effects on survival of adjuvant treatments, including pre- or postoperative systemic or postoperative intra-arterial chemotherapy, are currently under evaluation.

Key words: adjuvant chemotherapy, colorectal cancer, liver metastases, surgery

Introduction

Nearly half of the patients with colorectal adenocarcinoma will develop liver metastases, which represent the major cause of death. Untreated, these lesions have a poor prognosis with a median survival ranging from 4 to 21 months, and a three-year survival below 3% [1]. Palliative systemic chemotherapy improves quality of life but has little impact on survival [group ASCO 1999]. Retrospective studies have reported 0% to 2% five-year survival for patients with untreated but potentially resectable liver metastases vs. 25% to 28% for resected patients [2-4]. Despite much bias inherent to such retrospective comparisons, it appeared that surgical resections were able to ensure long-term survival in 25% to 30% of patients. Surgical resection should be discussed in every case, but should only be proposed when all metastatic disease can be removed. Preoperative assessment is then essential in the selection of patients for surgery. The goals of surgery are to remove all macroscopic liver deposits while preserving non-tumorous liver with minimal mortality and morbidity. The improvements in patient selection and surgical technique now allow liver resections with low mortality-morbidity rates and five-year survival approaching 30%. However, the wide range of survival follows several well-established prognostic. Hepatic recurrences occur in nearly two thirds of the patients and are sometimes amenable to repeat resections. New treatment modalities including chemotherapy, local destruction and radio-surgical techniques are currently under evaluation to improve the overall picture of treatment of liver metastases.

In this review we propose to summarise the knowledge on the surgical treatment of liver metastases from colorectal cancer and to discuss some modalities that may affect the management of this disease in the near future.

Selection of patients for surgery

Patient

Standard clinical and anamnestic criteria, briefly summarised in the ASA score, should be used to determine if the patient is suitable for a general anaesthesia and surgery with potential bleeding. Special attention is given to the cardio-circulatory status as clamping manoeuvres of hepatic pedicle and vena cava may be used during the hepatic resection. It is important that coagulation profile be assessed since a transient decrease in vitamin K-dependant clotting factors and an increase in plasma fibrinogen concentration and fibrinogen degradation products may accompany major resections [5].

Liver function

The hepatic functional reserve should be sufficient to ensure postoperative liver function. If liver parenchyma
is normal, up to six anatomical segments or 75% of the volume of the liver can be resected without inducing post-operative liver failure. The absence of underlying disease and the functional capacity of the liver can be assessed by hepatic biological blood tests (AST, ALT, alkaline phosphatases, gamma GT) and by the classic Child and Pugh classification. Liver function tests such as indocyanin green (ICG) or C14-aminopyrin tests may theoretically help to evaluate the liver function preoperatively. However in non-cirrhotic patients, these data are not predictive of the risk of post-operating liver failure [6]. A trans-cutaneous needle biopsy of non-tumorous liver may be helpful to assess the status of liver parenchyma. In metastatic disease, liver parenchyma is rarely fibrotic or cirrhotic but can have been damaged by previous chemotherapy. Recent data have demonstrated that prolonged systemic chemotherapy could induce steatosis, portal or peri-portal fibrosis, micro-vascular changes such as peliosis or sinusoidal congestion [7]. These vascular changes can be responsible for increased risk of bleeding during surgery [8].

Control of primary and extra-hepatic tumour sites

When metastases are discovered during the follow-up after resection of a colorectal cancer, absence of recurrence at the site of the primary tumour should be checked. A rectal digital examination, a colonoscopy to eliminate Anastomotic recurrence or a new colic cancer checked. A rectal digital examination, a colonoscopy to

Hepatic involvement

Incomplete resection of intra-hepatic metastases is not associated with any clinical benefit, does not prolong survival [11, 12] and therefore should not be performed. An accurate localisation of all intra-hepatic lesions is essential to plan an adequate type of resection.

Trans-abdominal ultrasound has a low sensitivity for the detection of lesions less than 1 cm but is helpful to determine the relations between deposits and the intra-hepatic vessels and the vena cava.

Bolus dynamic computed tomography has a good sensitivity and allows a good appreciation of the volume of the non-tumorous liver parenchyma, giving helpful information to decide which type of resection should be performed [13–15]. Helical CT scans with CT images obtained during the portal venous phase following intra-venous contrast administration has a sensitivity exceeding 80% for the detection of liver deposits with a good specificity.

CT arterial-portography [16] obtained during the portal venous phase following a superior mesenteric angiography is more sensitive, but is invasive. Overall sensitivity for detection of small liver metastases exceeds 90% but perfusion abnormalities and pseudo-lesions are frequently observed reducing the specificity of the test [17].

Magnetic resonance imaging (MRI) is less invasive. Sensitivity was considered inferior to that of arterial portography but the use of super-paramagnetic iron oxide particles coupled with more powerful computers has markedly increased its sensitivity [18–20].

Intra-operative exploration

The exact role of laparoscopy used alone or in combination with laparoscopic ultrasound is not yet fully evaluated, but recent studies have suggested that it could be helpful in some cases either to avoid unnecessary laparotomy or to adapt abdominal incision to the extent of resection [21].

During laparotomy, a careful exploration of the abdominal cavity is performed. The gastro-intestinal tract and the site of the primary tumour are examined. The diaphragm, the paracolic gutters and the Douglas pouch are palpated, looking for peritoneal deposits. The routes of lymphatic drainage of the primary tumour are exposed and palpated, such as the origin of the inferior mesenteric artery for a left colonic or rectal cancer. The celiac axis and the hepato-duodenal ligament are explored. If lymph nodes or peritoneal deposits are found, specimens should be taken for frozen sections. The presence of metastatic lymph nodes in the porta hepatitis and the celiac region considerably worsens the prognosis but should not be considered an absolute contra-indication to resection, in particular if they can be completely removed. Five-year recurrence-free surviving patients have been reported in such cases [22].

Intra-operative ultrasonography

Intra-operative ultrasonography can detect small intra-parenchymatous lesions and thus modify the initially planned operation [23]. In terms of sensitivity and specificity, intra-operative ultrasonography for liver metastases detection is significantly better than surgical exploration and pre-operative ultrasonography [24] and comparable to computed arterial portography for sensitivity. In a comparative prospective study, detection
rates for liver metastases were 89% with a combination of ultrasonography and computed tomography arterial portography, vs. 96% for intra-operative ultrasonography [25].

Per-operative ultrasonography improved the surgical treatment in 11% to 30% of patients operated for liver tumours [23, 26, 27]. It can also guide fine needle biopsies, clarify the nature of detected lesions and give a precise mapping of the anatomical relations of the metastases to the main vessels [28].

Surgical resection

Choice of operation

The goal of surgery for liver metastases is to remove all the metastatic sites with free margins of at least 1 cm. The type of liver resection is not by itself a prognostic factor. The extent of liver resection depends on the size, number, location and relation of the metastases to the main vascular and biliary pedicles, and on the volume of the liver parenchyma to be left in place after surgery. Small metastases located near the liver capsule can be resected with wedge resections, whereas larger lesions often require anatomical resections. However, it may be necessary to perform a major liver resection to remove a centrally located small solitary metastasis. In some cases the choice is between several wedge resections and a major liver resection removing all the deposits at once. The first solution preserves more normal liver parenchyma but the cut section of the liver may be larger increasing the risk of bleeding. A major liver resection allows a better free margin between the tumour and the cut section of the liver and a better control of intra-hepatic vessels, but removes more parenchyma. The risk of post-operative hepatic failure and the theoretical risk of promoting the development of dormant liver metastases, by the mechanisms involved in liver regeneration [29], are increased.

Timing of liver and intestinal surgery for synchronous metastases

Resection of primary tumour and liver metastases can be either synchronous or delayed. In the majority of cases it seems preferable to delay the hepatic resection. The abdominal wall incision is usually different for the colorectal and the liver resection; bowel section and subsequent peritoneal contamination can favour the infection of a peri-hepatic or sub-phrenic fluid collection, hemodynamic changes and portal hypertension subsequent to vascular clamping can be detrimental to the viability of digestive sutures. In a large multicentric study [11], the postoperative morbidity was significantly increased when both resections were performed simultaneously (6.1% vs. 2.4%). However, some have reported one-stage procedures without added morbidity in selected cases [12]. The most common approach is to remove metastases simultaneously if they require a minor hepatectomy and are accessible through the same incision. In the other cases, the liver resection is postponed and realised two to four months later. During this period systemic chemotherapy can be administered.

Liver resection

Bleeding during or after surgery increases post-operative mortality and morbidity [30, 31]. In order to reduce blood loss several methods of vascular clamping have been proposed [32–37]. A normal liver can tolerate the induced normothermic ischaemia for 90 min with good clinical and biological tolerance [38]. Complete vascular exclusion of the liver, including the clamping of the hepatic pedicle and the infra and supra-hepatic vena cava, allows safe resection of large tumours or tumours close to the main hepatic veins or the vena cava [38–41]. Vascular pedicles can either be divided inside the liver during the division of the parenchyma or during the preliminary dissection of the porta hepatis. The liver tissue can be divided using a Kelly forceps or other devices such as an vibrating ultrasonic dissector [42]. Vessels and bile ducts are occluded by metal clips, and ligated or stapled according to their size. Suture ligations, application of fibrin tissue-adhesive sealant or Argon beam coagulation secures hemostasis of the cut liver surface. At the end of the operation a cholangiography can be performed to control biliary pedicles. Drainage of the sub-diaphragmatic space is generally left in place after major resection [43].

Results of surgery

Post-operative complications

In the absence of complications the mean hospital stay after liver resection averages 10 to 15 days. The improvements of anaesthesia and techniques of surgical resection had a significant effect on the decrease of the mortality and morbidity rates [44, 45, 46, 47]. In most studies, in-hospital mortality is less than 5% and is strongly influenced by per-operative blood loss, pre-operative liver function and extent of liver resection. Delayed liver and multi-organ failure may occur after major or extended hepatectomy [48]. Morbidity after resection of liver metastases ranges from 20% to 40% [11, 12, 49] and is usually due to transient liver failure, haemorrhage, sub-phrenic abscesses or biliary fistula (Table 1). Associated diseases such as diabetes or chronic pulmonary disease increase the risk of post-operative complications [44, 50].

Long-term results

Following surgery, five-year survival rates ranged from 25% to 40% [12, 51–53] (Table 2). In a large series of 350
Table 1. Complications of liver resections for metastases [11, 46, 69, 87].

<table>
<thead>
<tr>
<th>Liver-related complications</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-hepatic fluid collection or abscess</td>
<td>5-10</td>
</tr>
<tr>
<td>Bile leak</td>
<td>3</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1-5</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1-2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>1-3</td>
</tr>
<tr>
<td>Intra-abdominal sepsis</td>
<td>1-3</td>
</tr>
<tr>
<td>General complications</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2-5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2-5</td>
</tr>
<tr>
<td>Deep ven thrombosis-pulmonary embolism</td>
<td>1-2</td>
</tr>
<tr>
<td>Cardiac failure, myocardial infarction</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Results of surgery.

<table>
<thead>
<tr>
<th>n</th>
<th>Mortality (%)</th>
<th>Morbidity (%)</th>
<th>Survival (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>years</td>
</tr>
<tr>
<td>Nordlinger 1987 [88]</td>
<td>80</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Scheele 1991 [12]</td>
<td>207</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Doci 1991 [89]</td>
<td>100</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td>AFC 1992 [22]</td>
<td>1818</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Fong 1999 [90]</td>
<td>1000</td>
<td>2.8</td>
<td>37</td>
</tr>
<tr>
<td>Harmon 1999 [91]</td>
<td>110</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>Minagawa 2000 [92]</td>
<td>235</td>
<td></td>
<td>38</td>
</tr>
</tbody>
</table>

patients who have had a potentially curative liver resection for colorectal metastases, the actuarial 5, 10 and 20 years survival rates were 39%, 23% and 17% respectively, with a 33.6% tumour-free survival rate at five years [46]. In the largest retrospective multicentric trial assessing the results of hepatic resections in 1818 patients with liver metastases of colorectal metastases, overall survival was 41% at three years and 26% at five years. Five-years survival was 28% in 1588 patients who had a resection of isolated colorectal liver metastases and 15% in 250 patients who had resected liver and extra-hepatic metastases. None of the 77 patients who had a palliative resection survived five-year [11]. In a multi-institutional study from the American Registry of Hepatic Metastases that included 607 patients that underwent a curative resection of liver colorectal metastases, the five-years survival rate was 33% and the five-years disease-free survival rate was 25% [54].

Recurrences are observed in 2/3 of the patients [11, 54, 55] and occurs within 12 months in 66% of cases [56-59].

Table 3. Prognostic factors [68].

<table>
<thead>
<tr>
<th>Factors</th>
<th>T3</th>
<th>N+</th>
<th>Free interval</th>
<th>n &gt; 4</th>
<th>Marge &lt; 1 cm</th>
<th>CEA level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 30 µg/l</td>
</tr>
<tr>
<td>1 pt</td>
<td>1 pt &lt; 2 years</td>
<td>1 pt</td>
<td>1 pt</td>
<td>1 pt</td>
<td>1 pt</td>
<td>2 pts</td>
</tr>
</tbody>
</table>

Two-year survival

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 pts</td>
<td>&lt; 5 pts</td>
<td>&gt; 5 pts</td>
</tr>
<tr>
<td>78%</td>
<td>59%</td>
<td>44%</td>
</tr>
</tbody>
</table>
pective series of 1568 patients with resected liver metastases from carcinoma [68]. Two- and five-year survival rates were 64% and 28%, respectively, and were affected by CEA level, stage of the primary tumour, disease-free interval, number of liver nodules and resection margin. Giving one point to each factor, the population was divided into three risk groups with different two-year survival rates: 0–2 (79%), 3–4 (60%), 5–7 [43%]. Another risk score for recurrence following liver resection for colorectal metastases was established by multivariate analysis of a series of 456 patients [69].

These data suggests that patients who underwent a surgical resection with a tumour-free surgical margin, have increased survival regardless of other prognostic factors.

Repeat liver resections

Recurrences are observed in 2/3 of operated patients, half of them occurring in the liver. The role of occult metastases or dormant cancer cells, which later developing into patent metastases, has been established in an experimental model [29].

Recurrences limited to the liver, following previous hepatic resection are amenable to iterative resection [70–72]. Such recurrences occur in 25% to 53% of the cases [70, 73, 74]. Post-operative mortality and morbidity do not differ from those reported after a first resection and the mean survival approaches two years [72, 74, 75]. In a series including 146 patients with intra-hepatic recurrence following hepatectomy treated by repeat liver resection the actuarial survival rate was 78% at one year, 30% at three years, 16% at 5 and 10 years, comparable to that observed following primary liver resections [73]. Hepatic recurrences should therefore be resected whenever possible.

How to improve results

To date, surgical resection is the best treatment for hepatic metastases. However, only 10% to 20% of the patients fulfill selection criteria and are amenable to surgery. New modalities including portal vein embolisation, local destruction and chemotherapy aim to increase the number of patients that can be resected, therefore improving the overall results of treatment of liver metastases.

Portal embolisation

A technically feasible curative liver resection might be contra-indicated because the volume of the remnant liver, as measured by volumetric CT scan, will be too small to ensure a good hepatic function (i.e. inferior to 20% of the volume of the non-tumorous liver). In some of these cases, a pre-operative portal venous branch embolisation can be performed in order to induce an atrophy of the lobe to be removed and a compensatory hypertrophy of the lobe that will be left in place. A gelfoam-gentamicin powder and N-butyl-2-cyanoacrylate with lipiodol are used to perform portal embolisation, usually by percutaneous trans-hepatic access under ultrasonographic control. Hepatic volume is checked every two weeks by computed tomography volumetry. The resection is generally performed three to six weeks after the embolisation when morphological control shows an adequate hypertrophy of the remaining liver parenchyma. Selective portal embolisation is performed with a 90% technical success rate and may lead to a 20% to 50% hypertrophy of the remnant lobe, with minimal morbidity and without inducing increased post-operative complication [76–79].

Local destruction (Table 4)

Therapies such as cryotherapy or radiofrequency ablation attempt to destroy tumours in situ. The efficiency of these new treatment modalities have not yet been tested in randomised trials and their use should be restricted to the treatment of otherwise non-resectable liver deposits.

Cryotherapy involves the freezing and thawing of liver tumours by means of a cryoprobe inserted into the tumour. During freeze/thaw cycles, ice formation occurs in an area termed iceball leading to tumour destruction. Cryosurgery is feasible for tumours up to 6 or 8 cm even if located near the main vascular pedicles. The size of the probe precludes percutaneous utilisation. Complications include haemorrhage, sub-phenic or hepatic abscess, bile collection or fistula, myoglobinuria. Radio-frequency ablation involves percutaneous or intra-operative insertion of an electrode into the lesion under ultrasonic guidance. RF energy is emitted through the electrode and generates extreme heat, leading to coagulative necrosis. RF is feasible for tumours less than 3 cm and some strategies can increase the treatment area up to 5 cm (multi-probe arrays, internal cooling of the electrode, vascular clamping…). Complication rate is very low, usually below 2%.

The effectiveness of cryotherapy and RF in destroying liver metastases has been demonstrated in several retrospective studies, but the long-term results and the beneficial effects on survival are not yet proven.

Regional therapies can be used as palliative treatment for non-resectable lesions or can be associated with surgical resection.

<table>
<thead>
<tr>
<th>Time/lesion</th>
<th>Diameter</th>
<th>Multiples lesions</th>
<th>Per cutaneous</th>
<th>Morbidity</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>—/—</td>
<td>5–10 cm</td>
<td>simultaneous</td>
<td>+/—</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>&gt;20 min</td>
<td>&lt; 3 cm</td>
<td>consecutive</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 4: Local therapies.
In a prospective, non-randomised study, radiofrequency was used in 123 patients with histologically confirmed, unresectable hepatic malignancies without extra-hepatic disease. The mortality and morbidity rates were 0% and 2.4% respectively. With a median follow-up of 15 months, secondary lesions recurred at the site of local destruction in only 3% of patients. New hepatic or extra-hepatic disease developed in 30% of patients, the liver being the first site of recurrence in 80% of these patients [80].

Peri-operative chemotherapy

To date, surgical resection alone is the standard treatment for patients with resectable liver metastases. The benefit of adjuvant chemotherapy has not been clearly proven. A German multicenter trial failed to demonstrate any benefit of an adjuvant postoperative arterial treatment using 5-FU and folic acid [81, 82]. Two recent studies using adjuvant hepatic arterial infusion of FUDR and systemic chemotherapy after resection of liver metastases demonstrated a significant improvement in three-year recurrence-free survival compared with surgery alone and an improved two-year survival rate after HAI and systemic chemotherapy compared to systemic chemotherapy alone [83]. These results are encouraging for the future but the significant toxicity, cost, patient and centre selection, and the absence of long-term survival benefit may limit the widespread use of this therapy.

Systemic chemotherapy using SFU in combination with newer drugs such as oxaliplatin or CPT-11 can reduce the volume of liver metastases [84, 85]. One objective of chemotherapy can therefore be to render resectable liver metastases previously considered to be non-operable. In one study systemic chemotherapy permitted surgical resection of liver metastases in 16% of patients previously considered to be non-resectable because of their location, size, number, or the association with extra-hepatic disease. There was no operative mortality. The cumulative three- and five-year survival rates were 54% and 40%, comparable to those observed after surgical resection of resectable lesions. Hepatic recurrence in 34 patients was amenable to repeat surgery in 15 cases. [86].

These results questioned the role of neo-adjuvant chemotherapy before liver resection in resectable lesions. A multi-institutional intergroup randomised prospective trial was recently initiated by EORTC to demonstrate the impact of preoperative systemic chemotherapy on resectability, disease-free survival and overall survival for patients with resectable liver metastases.

Conclusion

The field of surgery of liver metastases is evolving rapidly. The proportion of metastases resected is increasing with surgeons becoming more aggressive, encouraged by results of treatment. Some unresectable deposits can now be destroyed by local ablation techniques used during surgery or percutaneously. Some metastases can shrink and become resectable after administration of chemotherapy.

However, in spite of the excitement inspired by such progress we must not forget that most of these techniques have not yet been validated and we must organise well-prepared clinical trials to demonstrate that they can have an impact on survival of the patients.

References


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