Strategies to Increase the Resectability of Liver Metastases from Colorectal Cancer

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Abstract
Liver resection can provide long-term survival and cure for patients with colorectal liver metastases but is feasible in only 15–25% of patients. In the last few years several major developments have contributed to increase this resectability rate. Neo-adjuvant chemotherapy can provide response rates as high as 50%, allowing surgery in about 10–15% of patients initially deemed unresectable. Patients requiring extensive liver resections with an anticipated small residual liver volume can undergo portal vein embolization to reduce the risk of postoperative liver failure by inducing hypertrophy of the remnant liver. Extensive bilobar disease can be treated by two-stage hepatectomy, with an interval to allow liver regeneration. Ablation techniques can be combined with hepatic resection to reduce local recurrence from incomplete surgical resection margins or to destroy contralateral tumor deposits. Finally, for patients with tumors involving the inferior vena cava or the hepatic veins, in which conventional resection is not feasible, in situ hypothermia or bench resection with reimplantation are suitable for very selected patients. Downstaging strategies may increase the resectability rate of colorectal liver metastases by over 20%.

Introduction
Colorectal cancer is one of the commonest malignancies with about 700,000 new cases diagnosed each year worldwide [1]. Of these approximately 60% will eventually develop metastatic disease [2], which is confined to the liver in half of these patients [2, 3].

In 1978 Foster [4] collected a multicenter series of 168 patients undergoing hepatic resection for colorectal liver metastases (CLM) and reported a 20% 5-year survival. Since then many studies have confirmed that surgery is an effective and curative treatment for CLM, with 10-year survival rates between 20 and 26% [5–8]. These results contrast sharply with the outcome of patients with nonresectable disease. Chemotherapy can only marginally prolong life expectancy, and 5-year survival in untreated patients is negligible [9, 10]. The natural history of untreated patients with CLM has been studied, but very few reports have taken into account the extent of hepatic involvement showing that survival was markedly shorter in patients with bilobar CLM than in those with solitary
Table 1. Downstaging systemic chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Regime</th>
<th>Other treatment</th>
<th>Number resected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wadler et al. [24], 1989</td>
<td>30</td>
<td>5-FU-interferon-α</td>
<td>None</td>
<td>1 (3%)</td>
</tr>
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<td>Fowler et al. [25], 1992</td>
<td>n.a.</td>
<td>5-FU-leucovorin</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Bismuth et al. [29], 1996</td>
<td>330</td>
<td>Intravenous 5-FU-leucovorin-oxaliplatin</td>
<td>PVE</td>
<td>53 (16%)</td>
</tr>
<tr>
<td>Adam et al. [20], 2001</td>
<td>701</td>
<td>Intravenous 5-FU-folinic acid-oxaliplatin</td>
<td>PVE</td>
<td>95 (13.5%)</td>
</tr>
<tr>
<td>Albers et al. [32], 2001</td>
<td>33</td>
<td>Intravenous oxaliplatin-5-FU-leucovorin</td>
<td>Cryotherapy</td>
<td>9 (27%)</td>
</tr>
</tbody>
</table>

5-FU = 5-Fluorouracil; PVE = portal vein embolization.

or multiple unilateral lesions [11, 12]. Although a different and more aggressive biological behavior may be postulated in cases with extensive disease, it is unknown whether this will ultimately prevail over surgical enthusiasm in deciding the fate of patients with CLM.

Resectability is the limiting factor, being feasible in only 10–15% of patients with CLM [5]. However, to define resectability is not an easy task. Unfavorable localization, bilobar distribution and a large number of metastatic deposits may all preclude liver resection for CLM. More recently, some of these criteria have been questioned. The prognostic significance of bilobar involvement, for instance, is controversial. Some authors report bilobar disease to be a poor prognostic factor [13, 14], whereas others suggest that a bilobar distribution of lesions does not affect overall survival [15–17]. Several recent reports also suggest that hepatic resection should be attempted regardless of the number of metastases [8, 15, 18, 19]. Situations where an anticipated small residual liver might preclude surgery have also been resolved by the use of portal vein embolization and even the strictest contraindications to resection, such as extrahepatic disease and the impossibility to achieve clear resection margins, have been overcome by multimodal strategies including surgery and chemotherapy or surgery and cryoablation, respectively [20, 21].

Whether newer techniques for increasing resectability rates for patients with CLM will be associated with satisfactory long-term survival needs to be confirmed. Patients with resectable disease are a self-selected good prognosis group, whose outcome is considerably better than those who do not undergo resection [16, 22]. The state of the art for the resection of CLM is changing rapidly with the contribution of new chemotherapy regimes, interventional radiology and novel surgical techniques [20, 23].

This review analyses the various treatments which, alone or in combination, may increase the number of patients who might benefit from potentially curative surgical treatment. The data of this review are based on information from a Medline search for the period 1980 to November 2002.

### Downstaging Chemotherapy

Until recently only a few nonrandomized retrospective studies and case reports had been published in which unresectable CLM had been downstaged and made resectable by neo-adjuvant chemotherapy [24–26]. Regimes most commonly included 5-fluorouracil (5-FU), modulated by leucovorin or folinic acid, delivered either intravenously (table 1) or via the hepatic artery. Disease regression was observed in only 20% of cases with these regimes [27]. In the last decade, the advent of two other chemotherapeutic agents, the DNA topoisomerase-I inhibitor Irinotecan hydrochloride (CPT-11) [28] and oxaliplatin, a non-nephrotoxic platinum derivate, administered alone [9] or in combination with 5-FU [10], has resulted in response rates as high as 50% (fig. 1).

Bismuth et al. [29], in 1996, produced a stimulus to neo-adjuvant chemotherapy when they reported a series of 53 patients treated with systemic intravenous chemotherapy followed by liver resection. Chronomodulated (synchronized with a diurnal cycle) intravenous infusion through an implanted venous access port consisted of 5-FU (700–1,200 mg/m²/day), folinic acid (300 mg/m²/day) and oxaliplatin (25 mg/m²/day), lasted 4–5 days and was repeated every 2–3 weeks. The rationale of chronomodulation was to optimize dose intensities and tolerance of drugs by a treatment that is timed in a sinusoidal manner.
Resectability of Liver Metastases from Colorectal Cancer

along a 24-hour period with peak flow rates at 4 a.m. for 5-FU and folinic acid and at 4 p.m. for oxaliplatin [30]. In a multicenter randomized trial, a lower complication rate was observed with this protocol, when compared to standard treatment, as the incidence of mucosal toxicity dropped from 89 to 18% and peripheral sensory neuropathy occurred in only 14% of cases [31]. The series of patients undergoing surgical resection was from a group of 330 patients with unresectable disease, as defined by an experienced surgeon, because of ill-located, large or multiple CLM, or because of extrahepatic disease, who underwent this chemotherapy regime. In the surgical series of 53 patients (16%) there was no operative mortality and the complication rate was comparable to that observed in patients undergoing liver resection without preoperative chemotherapy. Overall 3- and 5-year survival rates were respectively 54 and 40%, but hepatic disease relapsed in 66% of cases after a mean follow-up of 42 months [29].

Five years later, in 2001, the same group confirmed and validated these results in a larger series comprising 701 patients with CLM, evaluated for liver resection and deemed ‘unresectable’ [20]. Following chemotherapy with 5-FU/leucovorin and oxaliplatin, 95 patients (13.6%) subsequently underwent a potentially curative liver resection. In this study [20], the overall actuarial 5-year survival was 34%. When divided by the different categories of initial nonresectability, the 5-year survival was 60% for large lesions, 49% for ill-located tumors, 34% for multiple lesions, and 18% for extrahepatic disease. However, a significant difference was noticed for different extrahepatic locations, as solid organ resectable disease was associated with a 36% 5-year survival, whereas lymph node involvement carried a dismal prognosis [20]. In the same year, Alberts et al. [32] reported a 50% response rate with the same regime, allowing surgical resection in 9 of 33 patients with unresectable liver only colorectal metastases.

The results from Bismuth et al. [29] are very encouraging, but reflect a very aggressive approach to metastatic disease from colorectal cancer. In both studies from the French group, the number and size of the lesions and, with the exception of regional lymph node involvement, even the presence of locoregional invasion were not absolute contraindications to surgery, providing complete resection with clear margins could be accomplished. In a limited number of patients with residual disease chemotherapy was continued postoperatively until a second stage could be performed. Cryotherapy was also used to clear small residual nodules not amenable to resection, or to treat a narrow resection margin. A portal vein embolization (PVE) was performed if the anticipated residual volume was less than 40% of the nontumorous liver volume. Finally, in patients with synchronous pulmonary metastases, lung resection was normally performed following liver surgery, after 2–3 courses of chemotherapy [20, 29].

These reports suggest that the traditional nihilistic approach to extrahepatic metastatic disease from colorectal cancer can be challenged, although spread to regional lymph nodes should remain an absolute contraindication to liver resection.

There is continual interest in intra-arterial chemotherapy (HAC) in the treatment of CLM [33–35]. Administra-
Table 2. Downstaging intra-arterial chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Regime</th>
<th>Other treatment</th>
<th>Number resected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gayral et al. [37], 1987</td>
<td>n.a.</td>
<td>5-FU</td>
<td>None</td>
<td>3</td>
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<tr>
<td>Maruo and Kosaka [26], 1994</td>
<td>n.a.</td>
<td>Intra-arterial 5-FU-cisplatin-5-FU-pirubicin</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Elias et al. [38], 1995</td>
<td>196</td>
<td>Intra-arterial 5-FU-mitomycin C or 5-FU-pirubicin</td>
<td>Portal vein embolization</td>
<td>9 (4.6%)</td>
</tr>
<tr>
<td>Link et al. [33], 1999</td>
<td>74</td>
<td>Intra-arterial 5-FU/FA ± mytomycin/mitoxantrone</td>
<td>None</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Meric et al. [34], 2000</td>
<td>383</td>
<td>Intra-arterial 5-FU or FUDR + leucovorin/miotomycin</td>
<td>RFA2</td>
<td>19 (4.4%)</td>
</tr>
<tr>
<td>Clavien et al. [35], 2002</td>
<td>23</td>
<td>Intra-arterial FUDR</td>
<td>Cryotherapy2</td>
<td>6 (26%)</td>
</tr>
</tbody>
</table>

1 In nonresponders to 5-FU.
2 At the time of liver resection.

ation of 5-FU or fluorodeoxyuridine (FUDR), via a catheter inserted into the hepatic artery, has been extensively studied as a palliative or adjuvant treatment, but there are few studies in the neo-adjuvant setting [33–35] (table 2). Response rates as high as 65% have previously been documented in patients with unresectable CLM, although randomized studies have not proved a survival benefit over systemic chemotherapy in patients with unresectable disease [36].

In 1995, Elias et al. [38] reported the use of HAC as a downstaging treatment. Only 9 of 192 patients (5%) with unresectable CLM were eventually resected and 5 of them were alive and disease-free 5 years from the beginning of treatment. In a similar study by Meric et al. [34], 383 patients with unresectable CLM were treated with 5-FU- or FUDR-based HAC delivered by an implantable pump. Of these, 22 patients (6%) achieved a complete or partial response sufficient to consider surgical resection, though this was feasible only in 17 (4.4%). Despite a 1-year survival rate of 83%, only 1 patient was disease-free 12 months after surgery, as 78% developed recurrence in the liver after a median time of 8.5 months, and 50% at extrahepatic sites after a median time of 7 months. Recently, Clavien et al. [35] published the results of neo-adjuvant HAC on a series of 23 patients with unresectable CLM treated with systemic 5-FU or Irinotecan prior to enrollment in the study. Following HAC, a partial response was documented in 9 patients (40%), with a reduction of more than 30% in the initial tumor volume, allowing liver resection in 6. Five of these were alive and disease-free at a median follow-up of 30 months, with actuarial survival of 100 and 50% at 1 and 3 years, respectively. In this study [35], HAC was used as a second-line treatment following failure to control disease by systemic chemotherapy, but the response rate of 40% was much higher than that observed by other authors in similar circumstances (11–26%) [39, 40].

There are a few theoretical benefits associated with HAC. CLM receive a preferential arterial blood supply [41], and are often confined to the liver [3]. Certain drugs, like floxuridine (FUDR), an active metabolite of 5-FU, are more effectively extracted by the liver during the first pass, resulting in high local concentrations with minimal systemic toxicity. Conversely, the hepatic extraction of 5-FU is delivery rate-dependent, with both hepatic and systemic clearance decreasing at higher doses, and this mechanism has been exploited to try and reduce the incidence of extrahepatic disease by causing an overflow of 5-FU into the systemic circulation [42]. An attempt to increase the efficacy of the standard HAC protocol with 5-FU/FA, by adding mitomycin and mitoxantrone, has also been reported [33]. The response rate in this study was 66% and hepatectomy became feasible in 9 of 74 patients (12%) after initial treatment with intra-arterial 5-FU/FA, alone (n = 3) or in combination with mitomycin and mitoxantrone (n = 6), 7 of them being alive at a mean follow-up of 19 months [33].

Technical problems, such as hepatic artery thrombosis and catheter occlusion or dislodgment, and drug-induced complications, like chemical hepatitis, biliary sclerosis and gastroduodenal ulcerations, occur in approximately half of patients treated with HAC [38]. In a recent study HAC was well tolerated in 48% of cases and quality of life was judged to be excellent in 52% [35].
Table 3. Portal vein embolization in CLM

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PVE to surgery days</th>
<th>FRLV % (mean) before</th>
<th>FRLV % (mean) after</th>
<th>% resected</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Baere et al. [49], 1996</td>
<td>22</td>
<td>32</td>
<td>19</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Azoulay et al. [50], 2000</td>
<td>30</td>
<td>63</td>
<td>26</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>Kokudo et al. [51], 2001</td>
<td>18</td>
<td>24</td>
<td>38</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>Elias et al. [52], 2002</td>
<td>68</td>
<td>30</td>
<td>n.a.</td>
<td>n.a.</td>
<td>13</td>
</tr>
</tbody>
</table>

PVE = Portal vein embolization; FRLV = functional residual liver volume.
1 This series includes 27 patients with liver metastases from other primary tumors.

Portal Vein Embolization

Even if the tumor is technically resectable, surgery may be contraindicated if the anticipated remnant liver is too small, because of the risk of postoperative liver failure [16]. In these circumstances preoperative selective PVE can produce atrophy of the affected lobe and compensatory hypertrophy of the contralateral side.

This atrophy-hypertrophy sequence was initially observed in rabbits following ligation of a main branch of the portal vein [43]. In 1990, Makuuchi et al. [44] were the first to utilize PVE in the clinical setting with the intent to initiate compensatory hypertrophy of the future remnant liver, thus preventing postoperative liver failure, in patients undergoing extended liver resection for hilar bile duct carcinoma. Since then PVE has been used to increase the safety of major liver resections in patients with hilar cholangiocarcinoma, gallbladder cancer [45–47], hepatocellular carcinoma [48], and liver metastases, mainly from colorectal cancer [49–52] (table 3).

In patients with CLM, it has been empirically determined that at least 25% of the total liver volume should be preserved following surgical resection [49, 53]. A larger residual volume of up to 40% may be required for a liver compromised by high-dose chemotherapy or underlying chronic liver disease [50, 51]. Accurate measurement of liver volume is therefore crucial and is commonly performed by CT [54, 55]. Volumetric assessment is necessary prior to and after PVE, and CT estimations of the...
Liver volume correlate well with real intraoperative volumes, despite potential sources of error (partial volume effect, respiratory phase) [46, 49, 54]. Volumes are calculated by multiplying the area of each cross-sectional liver image by the slice thickness (0.5 or 1 cm), and can be expressed either as a percentage [50, 51] or as an absolute value in cubic centimeters [55]. The standard technique measures the planned resection and total liver volumes, and estimates the total healthy normal liver by deducting tumor volume [56]:

\[
\text{FRLV ratio} = \frac{\text{Estimated FRLV}}{\text{TLV} - \text{tumor volume}} \times 100,
\]

in which FRLV is the functional residual liver volume and TLV is the total liver volume.

With multiple deposits the calculations can become more difficult and imprecise [53, 54], and an alternative method measures the future residual liver volume (FRLV) directly with CT and estimates the ratio FRLV/TLV with a formula [53]. Indeed, a close association between TLV and body surface area (BSA) has been determined (TLV = 706.2 \times BSA [m²] + 2.4) [57], and with this method a correlation between FRLV/TLV and outcome has been reported [53]. This method seems to be useful in the comparison of FRLV between patients as it is not influenced by tumor volume [58].

Although PVE has been used in clinical practice for more than 10 years, its underlying mechanism is poorly understood. PVE causes a rapid change in hepatic hemodynamics and a significant increase in portal pressure, similar to that observed after major hepatic resection [58]. Cessation of portal flow, which is presumed to have a hepatotrophic effect [59], induces apoptosis with occasional minimal necrosis in the embolized lobe [45]. Interestingly, apoptosis is more marked in the pericentral area, indicating that these hepatocytes may be more sensitive to changes associated with PVE, such as relative hypoxia [45]. Hepatocyte deletion is thought to lead to atrophy of the embolized liver, which in turn is followed by cellular hyperplasia and hypertrophy of the other side, as hepatocytes enter a highly active phase of proliferation within 2 weeks after PVE [45]. This response seems to be mediated by the same factors responsible for liver regeneration after heptectomy [51, 60]. Hepatocyte growth factor is the most powerful factor released from hepatocytes in response to priming factors after hepatocellular injury [61]. Other mitogenic factors are epithelial growth factor, transforming growth factor α (TGF-α) and cytokines like tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) [62]. Co-mitogenic factors have also been identified, like insulin [63] noradrenaline [64], triiodothyronine and retinoic acid, although the precise role of some of these has not been clearly defined [62]. Their synergistic action lead to gene induction and DNA synthesis with subsequent expansion of the hepatocytes clones [65], and may be counteracted by negative regulators, like TGF-β and IL-1β, when regeneration has occurred [66, 67].

PVE is usually performed as a local anesthetic procedure, percutaneously under ultrasound guidance, most commonly via a contralateral transhepatic approach to the portal branch to be embolized [49, 50] (fig. 2), but direct operative exposure of an ileocolic vein to allow portal vein access [44, 46, 68] and an ipsilateral approach [69] have also been described. Usually it is the right portal vein to be embolized, as the right lobe is usually several times larger than the left, but it is also possible to carry out a left PVE in patients requiring an extended left hepatectomy. Several embolizing agents have been reported (ta-
ble 4), but cyanoacrylate and Gelfoam® with Lipiodol® are those most frequently used in patients with CLM [49–52]. In particular, cyanoacrylate seems to induce a greater inflammatory response and has been associated with a lower recanalization rate than Gelfoam® [46].

The time necessary to induce maximum hypertrophy after PVE has not been clearly established. The time interval from PVE to resection varies and ranges from 3 [51] to 9 weeks [50]. In a series by De Baere et al. [49], 29 of 31 patients reached adequate hypertrophy by 4–5 weeks, in accordance with previous studies showing maximum regeneration in the first week after hepatic resection, and 70–80% of total regeneration in 1 month [70].

PVE is highly effective [71]. Adequate hypertrophy is achieved in the majority of patients with CLM, with an average increase in FRLV of approximately 14% of TLV [49–52] (fig. 3). As hypertrophy is also associated with a functional gain in the non-embolized lobe [72, 73], radiological, biochemical and hemodynamic parameters have been studied to predict the extent of regeneration. In 1998 Goto et al. [74] reported that the hypertrophy rate after embolization is predictable from the increase in the portal blood flow velocity, as measured by Doppler ultrasound the day after the procedure. The distinction between healthy and injured livers is important as chronically damaged livers are less able to regenerate [52, 58]. In a recent report from Wakabayashi et al. [58], multiple regression analysis revealed that the prothrombin time and FRLV/TLV ratio in normal liver were independent parameters predicting hypertrophy after PVE. In series of 84 PVEs, the largest to date, multivariate analysis indicated that diabetes mellitus, high bilirubin level and male gender were important cofactors associated with a reduced hypertrophy [46].

Successful PVE does not necessarily lead to surgical resection, 63 [50] to 96% [51] of patients subjected to PVE ultimately being resected. In a selected series of 30 patients with CLM, PVE was followed by a laparotomy in 28 patients, but hepatectomy was feasible only in 19 cases, as disease progression and extrahepatic spread precluded surgical treatment in the remainder [50]. In order to minimize the risk of tumor progression during the regeneration phase, it looks reasonable to administer a short course of chemotherapy following PVE. In our experience, we observed a decrease in tumor volume (from 150 to 130 ml, median values) in patients receiving post-PVE chemotherapy, an increase in tumor volume (from 238 to 322 ml, median values) in the non-chemotherapy group, and overall a similar increase in FRLV in the 2
groups [75]. These preliminary data suggest a role for interim chemotherapy as it might be beneficial to halt tumor progression without affecting liver hypertrophy.

PVE is usually well tolerated [49, 50]. Common side effects are minimal and include fever, nausea, mild abdominal pain and a transient abnormality of liver function tests [49–51]. In a review of about 350 PVEs for various conditions, there was no peri-procedural mortality and a major complication rate below 5%, including hemobilia, sepsis and the need for re-embolization [71]. Although unreported, bilateral or main portal vein occlusion remains a possible risk, especially during selective embolization of segment IV branches. Nagino et al. [76] recommend embolization of the right and segment IV portal vein branches when an extended right hepatectomy is planned. The intention is to increase segment I–III hypertrophy. A further potential benefit is to prevent accelerated tumor growth in segment IV, as previous studies in patients with bilobar lesions have suggested that the growth rate of metastases in the non-embolized lobe is faster than that of normal parenchyma following selective PVE [77]. In 2001 Kokudo et al. [51] also reported that a change in tumor volume in the embolized lobe was similar to a change in liver volume in the non-embolized lobe, having increased by 20.8 and 20.6%, respectively, in the first 3 weeks following PVE. In this study, the disease-free survival rate of the 18 patients in the PVE group was significantly poorer than in a control group of 47 patients who had undergone major hepatic resection for CLM without PVE (respectively, 15.2 and 0% at 2 and 4 years and 45.8 and 34.4% at 2 and 4 years). However the 2 groups differed with respect to maximum tumor diameter, which is known to be an important prognostic factor [78].

More promising results were reported by Azoulay et al. [50], in a series of 30 patients with CLM undergoing PVE, treated preoperatively with 5-FU/FA and oxaliplatin chemotherapy. In this series, PVE increased the feasibility of liver resection by 19% and the actuarial survival rate was 40% at 5 years, similar to that of patients who underwent resection without PVE (38%). Similar rates were recently reported by Elias et al. [52] in a group of 41 patients with CLM, where the majority had also received pre- and post-operative chemotherapy, and the 5-year survival was 37% and 5-year disease-free survival rate 21%. The improved results from the French authors [50, 52] may reflect a beneficial role for neo-adjuvant chemotherapy, as only 1 of the patients undergoing PVE in the study from Kokudo et al. [51] received preoperative chemotherapy.

PVE does not appear to increase the risks associated with major liver resection [49–52]. A perioperative mortality of less than 5% and a complication rate ranging between 7 [50] and 27% [52] are comparable to those reported in patients not subjected to PVE [16, 18, 78].

Although PVE has proved to be effective in increasing the resectability of patients with CLM, its positive effects on hepatic function and regeneration must be weighed against the potential risk that this procedure may promote oncogenesis. Further studies are needed to evaluate the role of adjuvant chemotherapy in patients undergoing PVE.

Two-Stage Hepatectomy

Patients deemed unresectable because of extensive bilobar disease may be treated by a ‘two-stage hepatectomy’. Surgery is contraindicated if complete resection cannot ultimately be achieved. This relatively new approach involves complete resection of the tumor in one lobe, leaving the tumor in the contralateral lobe to be removed at a second resection. The rationale is to minimize the risk of liver failure by performing a second and complete resection once regeneration has occurred. The second hepatectomy is performed only if it can be potentially curative, after re-staging of metastatic disease has excluded significant tumor progression and when adequate parenchymal regeneration has occurred (fig. 4).

The only study to date on two-stage hepatectomy for CLM comes from Adam et al. [79] who, in 2000, reported a series of 13 patients with bilobar involvement treated by a two-stage resection. Prior to this, the term ‘two-stage liver surgery’ had been applied to a single hepatic resection for advanced metastatic liver disease, which had been preceded by a laparotomy and ligation of the portal vein branch supplying the affected lobe [80].

The series on two-stage hepatectomy reported by Adam et al. [79] represented 3% of 398 patients with unresectable disease because of bilobar involvement. Unfavorable location, size or large number of metastases were the initial reasons to preclude a one-stage resection, and the expected residual liver did not reach adequate volume, even after PVE. All patients but 1 received systemic chemotherapy after each hepatectomy, and this was commenced 3 weeks after surgery to minimize the inhibitory effect of antineoplastic drugs on liver regeneration. The rationale for adjuvant treatment in this context is to halt tumor progression, as growth factors involved in the hypertrophy of the remnant liver can also boost tumor
growth, as demonstrated by studies following liver resection [81, 82] and PVE [77]. For the same reason, it may be advisable to carry out the smaller liver resection first, leaving the major hepatectomy to the second stage, thereby minimizing growth stimulation to the residual tumor. However, the relation between the tumor and large vessels must be considered, as disease progression may not allow a second stage, where metastases are close to major vascular structures.

To facilitate the second procedure, minimal dissection is recommended in the area of the liver to be resected at a second stage. The French experience suggests avoiding division of the corresponding triangular ligament and complete exposure of the vascular structures, to reduce the extent of fibrosis and adhesions [79].

The most appropriate timing of the second liver resection has not been established, but is selected as a function of liver regeneration and control of remnant liver tumor [79]. Performing the second resection 1–2 months following the first would allow over 80% of total liver regeneration [38].

Two-stage hepatectomy was successfully accomplished in 81% of cases in the study by Adam et al. [79], who reported a 3-year survival rate of 35%, and a median survival of 31 months after the second hepatectomy, but with a high perioperative mortality of 15%. This high perioperative mortality is not necessarily a consequence of repeat resection, as many studies have shown that the perioperative death rate is similar between first time and repeat hepatectomy for recurrence [83–85], though perhaps with longer intervals between the first and second liver resection. Morbidity and mortality in this cohort may have been due to an aggressive multidisciplinary approach, including chemotherapy, PVE and also cryotherapy.

This approach extends the indications for surgical resection in patients with bilobar CLM.

The real benefit of this procedure, however, has been questioned as only 4 of 398 patients with initially unresectable CLM are reported to be disease-free at 5 years following two-stage hepatectomy. On the other hand, it is promising to observe that long-term remission may be achieved in patients otherwise destined to a very poor outcome.

The role of chemotherapy in candidates for two-stage resection needs to be clarified, and the risk-benefit assessment must take into account the possibility of higher perioperative risk and lower long-term survival than patients conventionally considered for resection.

**Local Ablation Techniques**

A large proportion of patients with metastatic disease from colorectal cancer have metastases confined to the liver [3]. The excellent results with surgical resection of CLM has led to the development of a variety of local ablation techniques, like cryotherapy, radiofrequency ablation (RFA), interstitial laser photocoagulation (ILP), microwave ablation and electrolysis. All these modalities have been used to palliate CLM, especially in patients with a small number of relatively small metastases and no extrahepatic disease. The experience of these techniques...
Table 5. Results of surgical resection combined with cryotherapy for CLM

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Survival median</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>5 years</th>
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<tr>
<td>Shafir et al. [96], 1996</td>
<td>25</td>
<td>–</td>
<td>74</td>
<td>55</td>
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<tr>
<td>Adam et al. [87], 1997</td>
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<td>–</td>
<td>77</td>
<td>52</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Weaver et al. [95], 1998</td>
<td>136</td>
<td>30</td>
<td>–</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Wallace et al. [89], 1998</td>
<td>52</td>
<td>20</td>
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<td>Seifert and Morris [97], 1998</td>
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<td>Ruers et al. [94], 2001</td>
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1 Some of these patients had cryotherapy alone.
2 94% of the patients received intra-arterial chemotherapy.

in the downstaging process to facilitate surgical resection is limited. Some of these techniques, however, have found application to increase resectability, when used as a complement to surgery and when hepatic resection by itself cannot be curative.

Cryotherapy is the ablation technique with the longest track record and the development of vacuum-insulated cryoprobes cooled by liquid nitrogen or argon, along with the application of intraoperative ultrasound to direct and guide the cryoprobes, has made this technique feasible and relatively simple to use [86]. Once the cryoprobe is inserted into the tumor, two freezing-thawing cycles are commonly required for each lesion, with the freezing time being dependent on the formation of an ice-ball, visible on ultrasound as a hypoechoic area surrounded by a hyperechoic halo [86, 87]. The main drawback of this modality is that a laparotomy is commonly required, making it unsuitable for patients with high anesthetic risk. With engineering improvement, cryoprobes as small as 3 mm in diameter have been constructed, allowing laparoscopic and even percutaneous cryoablation [88].

To date, many authors have reported its application during surgical resection of CLM to clear a positive or a narrow (<1 cm) surgical resection margin, or to ablate a residual tumor not amenable to resection [30, 89–91]. These intraoperative applications must be clearly defined. In cases where narrow resection margins were frozen to reduce the incidence of local recurrence, none was observed in a series of 15 patients undergoing hepatectomy for CLM [87]. The value of adjuvant cryotherapy in this situation is unclear as similar overall and disease-free survival rates have been reported in patients despite surgical resection margins of <10 mm [92]. Cryoablation has also been used to destroy tumor at the resection margins. In a recent study from Australia, edge cryotherapy was applied in 48 patients with involved resection margins (confirmed by the pathologist) following hepatectomy for CLM. Tumor recurred at the edge in 7 patients (14%) after a median follow-up of 39 months [91]. The local recurrence rate in a group of 9 patients, found postoperatively at histology to have positive resection margins, but not treated, was 48%, suggesting a role for cryoablation as an adjuvant tool [91].

The commonest application of cryotherapy in patients with CLM is the ablation of unresectable metastatic nodules [22, 86, 87, 89, 91, 93–96]. Where cryoablation has been used in combination with surgery (table 5), it is difficult to extrapolate its real therapeutic value. Two recent studies have evaluated the combination of surgery with cryotherapy and indicated that this combined strategy in patients with involved margin or surgically unresectable CLM may confer similar survival as resection alone in patients with clear margins [89, 91]. However, overall survival and disease-free survival do not equate. In a study on 30 patients where cryoablation was used as a complement to surgery to destroy CLM otherwise not resectable, survival at 1 and 2 years was 76 and 61%, but disease-free survival was only 35 and 7%, respectively, as more than two thirds of the patients had developed recurrent disease at a median follow-up of 26 months [89]. Most commonly disease recurs within the liver, and local recurrence at the site of ablation occurs in 5–44% of patients [86]. Recurrence has been found to be significantly greater when treating multiple lesions (>8) [89], large lesions (>3 cm) [87,97] and tumors situated close to major vessels, as the blood warmth may impair the freezing process [94]. The use of inflow clamping to facilitate tumor necrosis is controversial. Although the Pringle ma-
neuer is reported to increase the efficacy of cryotherapy, it will add an ischemic insult to the injury caused by the cryoprobe [87].

Cryotherapy is regarded as a safe procedure, but mortality rates as high as 4% have been reported [86, 98]. Cryoshock remains a critical but rare event following cryotherapy. It presents as a form of multiorgan failure with disseminated intravascular coagulopathy and acute renal failure, and accounts for approximately 18% of peri-procedural deaths [99]. Morbidity occurs in up to 30% of cases and includes hemorrhage, abscess formation, bile leak/collection, pneumonia and pleural effusion [86]. Some complications are specific to cryoablation. Cracking of the liver is seen with relative frequency (5–28%), but rarely results in significant hemorrhage. Hypothermia can be prevented with warming blankets and warmed intravenous fluid administration [100].

Unlike cryotherapy, the history of RFA and ILP is more recent and very little has been documented on their application as a downstaging modality in patients with CLM. With these modalities, heat is used to destroy the tumor and is generated by radiofrequency radiation or by converting photon energy, respectively. Small catheters or hollow needles are inserted into the target lesion under ultrasound, CT or MRI guidance, to allow the passage of electrodes or laser fibers. RFA and ILP can be delivered at laparotomy, by laparoscopy or percutaneously [22]. RFA has been used as an adjunctive procedure to liver resection, in an attempt to eradicate unresectable CLM [35, 52, 101]. In one retrospective study, ILP was administered preoperatively to 3 patients and was combined with neo-adjuvant systemic (n = 2) or intra-arterial chemotherapy (n = 1) to downstage unresectable CLM [102]. However, current data are limited, and it is impossible to draw any conclusion on the efficacy of thermal ablation in this context.

Lesion size is a critical factor to the success of local ablation by RFA or ILP. Although volumes in excess of 150 ml (6 cm in diameter) have been treated with ILP [103], complete ablation is reported in only 75% of cases even with lesions smaller than 2 cm [103]. The introduction of multiple, cooled-tip, radiofrequency electrodes offers promise of larger volume necrosis and more effective treatment, but further follow-up is necessary to evaluate its efficacy. Compared to cryotherapy, RFA is less expensive and less invasive and it is commonly performed percutaneously under ultrasound guidance as a local anesthetic procedure. In a study comparing RFA with cryoablation (both at laparoscopy), RFA was associated with reduced blood loss, shorter hospital stay but longer ablation times (60 vs. 15 min) and higher recurrence rate for lesions of >3 cm (38 vs. 17%) [101]. Unlike cryotherapy, RFA and ILP are frequently delivered percutaneously with a risk of needle tract seeding of approximately 3% [103]. This risk is common to all percutaneous techniques, and must be considered carefully if they are part of a neo-adjuvant program.

Whether local ablation techniques truly increase resectability rates of patients with CLM is difficult to evaluate, as the majority of reports include series with different types of tumor, different treatment protocols and different selection criteria for patients. When used as a complement to liver surgery, local ablation techniques must completely eradicate residual tumor and should not be used as a method of salvaging an inadequate surgical resection [90]. Incomplete resection of CLM has been shown to have little, if any, impact on survival [89, 103]. In this setting, surgery with local ablation should be limited to selected cases, as suggested by Adam et al. [87] who used cryoablation in 15% of patients undergoing hepatectomy for CLM, and exclusively in cases where resection could not remove the entire tumor by itself.

**In situ and ex vivo Liver Surgery**

Most CLM can be resected with traditional methods, also using inflow or total vascular occlusion (TVE) when needed [104, 105]. Hepatic inflow occlusion was initially described by Pringle [106] in 1908 to minimize intraoperative bleeding, and recent studies from Hong Kong have suggested that the upper limit of tolerance of liver to warm ischemia is 120 min with intermittent inflow clamping [107]. CLM involving the hepatic veins or inferior vena cava (IVC) may be impossible to resect by conventional techniques (fig. 5). A poorly planned attempt may result in profuse hemorrhage and/or air embolism [108]. In these circumstances, TVE can provide a bloodless operative field and minimize the need for perioperative blood transfusion [105]. TVE is not appropriate for routine use as a randomized trial (including benign and malignant liver tumors) comparing total vascular exclusion with hepatic inflow occlusion demonstrated that blood loss was similar in the 2 groups, and major hemodynamic changes and hospital stay were greater in the TVE group [109]. TVE reduces cardiac output as a result of decreased venous return [108]. The resulting hemodynamic instability can be overcome by clamping the supra-celiac aorta [110], but the use of veno-venous bypass avoids the risk of renal, intestinal and spinal cord isch-
As with inflow occlusion, TVE time is restricted by hepatic tolerance to warm ischemia. Although duration of warm ischemia up to 2 h without major detrimental effects has been reported [111, 113], TVE should not exceed 1 h [105, 114]. In situations where major vascular resection and reconstruction of the venous outflow with autologous vein or prosthetic grafts are required, or the expected ischemia time is longer than 1 h, TVE cannot be a safe option. This applies mainly to patients with CLM at the hepatocaval confluence or with extensive infiltration of the IVC. In these situations, the techniques of ex vivo liver surgery, pioneered by Pichlmayr et al. [115] more than 10 years ago, have offered the possibility to perform radical resections [108, 116–118]. The three techniques described can be categorized as in situ, ante situm and ex situ resection. These require the use of hypothermic liver perfusion and veno-venous bypass, and differ mainly in the extent the major vasculature is divided in order to achieve optimal mobility of the liver. In the in situ technique hepatic inflow and outflow are clamped as in TVE, but the liver is perfused with hypothermic (4°C) University of Wisconsin solution to optimize liver preservation and to extend the period of tolerable liver ischemia to 4 h [113, 117]. In the ex situ technique the liver is completely detached from its vascular connections and the tumor excision and vascular reconstruction are carried out on the bench prior to reimplantation [108, 118]. An alternative to the classic type of ex situ liver surgery is the ante situm, where the division of the hepatic pedicle is avoided, but the liver is exteriorized by sectioning the suprahepatic vena cava [119]. During the anhepatic phase, systemic as well as porto-systemic veno-venous bypass are commonly instituted to maintain cardiovascular balance [108].

Recently, Lodge et al. [108] reported their experience with ex vivo (n = 4) and in situ liver surgery in 8 patients with CLM involving the hepatic veins or IVC. Two perioperative deaths were recorded, 1 patient died subsequently of recurrent disease and only 1 patient was disease-free at the 9-month follow-up. These results compare well with a series of 10 patients undergoing ex vivo liver surgery for CLM reported by Oldhafer et al. [118] in 2000, in which only 1 patient (10%) was alive 13 months after surgery, and the median survival was 21 months and the perioperative mortality was 30%.

Increased surgical experience with liver transplantation and knowledge of hypothermic organ preservation have certainly contributed to the development of these techniques, which have been pioneered in transplant centers. These techniques are associated with far greater morbidity and mortality than conventional liver resection [116]. The development of irreversible liver failure after ex situ liver surgery can cause a serious ethical dilemma, as the only chance for survival might rely on liver transplantation [118]. However, under the current Eurotrans-
plant regulations, superurgent grafting is not allowed in such a situation, although liver transplant has been performed in a few cases as a salvage procedure [118].

Only a small proportion of patients may benefit from this very radical and invasive surgical approach. Miyazaki et al. [120] reported a 5-year survival rate of 22% after IVC resection in patients with liver metastases, but results are usually dismal with few long-term survivors [108, 116, 118]. Therefore, in very selected cases, the in situ or ante situm resection techniques should be considered for CLM involving the hepatic vein confluence or the retrohepatic IVC, whereas the indication for an ex situ liver resection with autotransplantation of the remnant liver should be contemplated only in exceptional circumstances [114].

Conclusions

In recent years several major developments have coincided to radically alter the surgical management of CLM. As the safety of liver surgery has improved, new drugs have allowed neo-adjuvant therapy to be considered for unresectable disease. Radiological intervention with PVE allows a larger residual liver volume, reduces the risk of liver failure and facilitates extensive parenchymal resections. Bilobar disease can be managed by two-stage resection which may be associated with increased operative risk but may produce satisfactory long-term survival rates. Local ablative therapies have mainly been used for palliation but are increasingly being applied to reduce recurrence in patients where surgery alone may be associated with a high risk of recurrence. Finally patients with tumors with extensive involvement of the hepatic veins or IVC may be candidates for in situ or ex vivo resection, although the preliminary data would suggest a high operative risk and reduced long-term survival.

The facilities to provide all available techniques for the surgical management of CLM are essential to offer an optimal service to these patients and are dependent on a well-informed and integrated team of interventional radiologists, oncologists, anesthetists and surgeons. The potential to increase resectability may allow a significant improvement in the cure of CLM. In our experience the downstaging strategies have increased the overall resectability rate of CLM by over 20%.

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Resectability of Liver Metastases from Colorectal Cancer

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