Chemotherapy-Associated Liver Injury: Impact on Surgical Management of Colorectal Cancer Liver Metastases

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ABSTRACT

Chemotherapy is integral to the management of patients with advanced colorectal cancer liver metastases. Due to their improved efficacy, modern regimens can sometimes convert unresectable disease to a resectable state. As chemotherapy is often administered prior to hepatic resection, adverse effects on the liver are increasingly being recognized. Investigators have identified a wide spectrum of effects on the underlying liver parenchyma, ranging from mild forms of steatosis to severe steatohepatitis and sinusoidal obstruction syndrome. As the histopathologic definitions of these changes evolve, studies have identified specific patterns of hepatic injury related to the various chemotherapeutic agents. The impact of these changes on perioperative outcome after partial hepatectomy remains controversial. Timing and duration of chemotherapy may play a key role and account for discrepancies in outcomes seen among studies. In this review, we provide an overview of the spectrum of chemotherapy-associated liver injury and discuss its relevance to perioperative management of patients undergoing hepatic resection of colorectal cancer liver metastases.

Chemotherapy is integral to the treatment of colorectal cancer liver metastases (CLM). In the era of 5-fluorouracil (5-FU)-based chemotherapy, tumor response rate and median survival for unresectable patients were approximately 20% and 11 months, respectively.1 Even with marginally effective chemotherapy, hepatic resection yielded 5-year survival rates of 25–40%.2-4 Modern regimens which combine 5-FU with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) boast tumor response rates over 50%, thus extending survival of unresectable patients to 22–24 months.5,6 Combination of resection and modern chemotherapy is associated with 5-year survival approaching 60% in selected patients.7,8

A recent prospective randomized controlled trial compared outcomes of patients treated with perioperative FOLFOX (six cycles) and surgery (n = 159) versus surgery alone (n = 170). The combined treatment group had increased 3-year progression-free survival (35.4 vs. 28.1%, P = 0.058).9 However, along with improved efficacy and outcomes, modern chemotherapy can exert adverse side-effects on the liver, including fatty change (steatosis), steatohepatitis, and veno-occlusive disease termed sinusoidal obstruction syndrome (SOS).10-12

We herein review these potential chemotherapy-related liver injuries, their impact on surgical outcomes, and in turn implications for surgical management of CLM. Electronic databases including MEDLINE/Pubmed were interrogated using the following search terms: “colorectal cancer,” “chemotherapy associated liver injury,” “steatosis,” “steatohepatitis,” “sinusoidal obstruction,” and “outcomes.” Inclusion criteria were: (1) English language, (2) subjects with colorectal liver metastases, and (3) primarily addressing pathologic assessment of liver injury or outcome following chemotherapy.

CLASSIFICATION OF HEPATIC INJURY

Fatty liver disease (steatosis) is a growing concern in Western society. Autopsy reports suggest that 6–11% of the general population have fatty changes.13,14 Compared with normal histology (Fig. 1a), retained lipid is stored in micro- or macrovesicles, which displace the cytoplasm of hepatocytes, resulting in altered cellular function (Fig. 1b).15 Severity of steatosis is histologically graded by
the percentage of hepatocytes containing fat inclusions compared with all hepatocytes (mild <30%, moderate 30–60%, severe >60%).16 Steatosis has traditionally been associated with heavy alcohol consumption, but nonalcoholic fatty liver disease (NAFLD) contributes to its rising prevalence. Obesity, diabetes mellitus type 2, hypothyroidism, metabolic syndrome, and various drugs and toxins are contributing factors.17 Compared with normal liver (Fig. 2a), steatosis produces a characteristic yellow appearance (Fig. 2b).
Steatohepatitis represents the next stage of liver disease. Key histologic features include steatosis, lobular inflammation, and ballooning of hepatocytes (Fig. 1c). Steatohepatitis not related to alcohol consumption is termed “nonalcoholic steatohepatitis” (NASH), or “chemotherapy-associated steatohepatitis” (CASH) if related to chemotherapy. Although the pathogenesis is not entirely understood, the “two-hit” theory suggests that steatosis constitutes the first hit, while the second hit involves oxidative stress that causes lipid peroxidation, endotoxin-mediated cytokine release, and development of necroinflammation. The mechanism of chemotherapy-induced hepatic injury is thought to be secondary to production of reactive oxygen species, intended to induce tumor cell apoptosis. Previously steatotic livers seem most susceptible due to impaired regenerative capability and abnormal innate immunity. Kleiner et al. developed a reproducible pathologic grading system for steatohepatitis (Table 1).

Sinusoidal obstruction syndrome (SOS) is another chemotherapy-associated finding. Histopathologic features include edema of centrizonal hepatocytes, dissection of cell cords, and fibrotic sinusoidal occlusion, causing erythrocyte congestion at the level of hepatic sinusoids (Fig. 1d). More severe vascular toxicities include hemorrhagic centrilobular necrosis and regenerative nodular hyperplasia. SOS is semiquantitatively graded by the amount of sinusoids involved (mild: <1/3, moderate: 1/3 to 2/3, severe: >2/3). Macroscopic evidence is characterized by blue liver discoloration (Fig. 2c).

CHEMOTHERAPEUTIC AGENTS AND ASSOCIATED HEPATIC INJURY

Not all patients exposed to chemotherapy develop substantial liver injury (Table 2), but few risk factors have been identified. Metabolic disturbances such as obesity, diabetes mellitus, and hyperlipidemia have been directly linked to steatosis and higher degrees of NAFLD. These common comorbidities may increase susceptibility to further liver injury from chemotherapy. Brouquet et al. found that both body mass index (BMI) >27 kg/m² and hyperglycemia were independently associated with development of steatosis, steatohepatitis, and SOS.

5-Fluorouracil (5-FU), which remains the backbone of modern chemotherapy, has been linked to development of steatosis. As early as 1990, Zeiss et al. reported patchy fatty changes in segments regionally treated with its analogue floxuridine. Other reports indicate development of steatosis in 40–47% of patients after 5-FU therapy, although some changes may be reversible.

Addition of oxaliplatin and irinotecan has led to increased hepatic injury due to their specific toxicity profiles and increased use of chemotherapy in general. Table 2 summarizes liver injury rates following treatment with modern chemotherapy regimens in current series. Fernandez et al. first demonstrated a significant increase in steatohepatitis scores and liver injury in patients treated with irinotecan or oxaliplatin, as compared with 5-FU alone or no chemotherapy. Subsequently, Vauthey et al. assessed the pathologic effects of each drug separately by analyzing resection specimens. Irinotecan was independently associated with steatohepatitis and oxaliplatin with SOS (P = 0.001). Specifically, SOS was found in 19% of patients after receiving oxaliplatin, as compared with only 4% after irinotecan (P = 0.001). This confirmed the initial report by Rubbia-Brandt et al., who found SOS in up to 78% of patients receiving oxaliplatin. Similarly, in a study in which two-thirds of patients received oxaliplatin therapy, Karoui et al. reported that patients receiving chemotherapy had a higher rate of sinusoidal dilatation compared with controls (49 vs. 14%; P = 0.005).

Adding anti-vascular endothelial growth factor (VEGF) antibody bevacizumab may have a protective effect against oxaliplatin-induced sinusoidal injury. Ribero et al. reported a significantly lower incidence of sinusoidal dilatation in patients receiving oxaliplatin plus bevacizumab. Incidence of sinusoidal dilation of any grade reduced to half with this combination regimen (27 vs. 54%), and reduced to less than a third for severe (grade 2–3) sinusoidal dilatation (8 vs. 28%). These findings have been replicated by others.

### TABLE 1 NAFLD activity score (NAS) score for determining steatohepatitis

<table>
<thead>
<tr>
<th>NAS (points)a</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>Minimal (&lt;5%)</td>
<td>Mild (5–33%)</td>
<td>Moderate (33–66%)</td>
<td>Severe (≥66%)</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td>No foci per 200 × field</td>
<td>&lt;2 Foci per 200 × field</td>
<td>2–4 Foci per 200 × field</td>
<td>&gt;4 Foci per 200 × field</td>
</tr>
<tr>
<td>Ballooning of hepatocytes</td>
<td>None</td>
<td>Few</td>
<td>Many</td>
<td>–</td>
</tr>
</tbody>
</table>

a NAS 0–2 = no steatohepatitis; NAS 3–4 = borderline steatohepatitis; NAS 5–8 = definite steatohepatitis

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### TABLE 2  Histopathologic liver injury associated with preoperative chemotherapy before resection of colorectal liver metastases

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Liver Resection, n</th>
<th>Preoperative chemotherapy</th>
<th>Histopathologic liver injury following chemotherapy</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Patients treated, n (%)</td>
<td>Agents used</td>
<td>Molecular targeted agents</td>
</tr>
<tr>
<td>Rubbia-Brandt</td>
<td>2004</td>
<td>153</td>
<td>87 (44%)</td>
<td>5-FU/LV;IRI; OX</td>
</tr>
<tr>
<td>Fernandez</td>
<td>2005</td>
<td>37</td>
<td>24 (65%)</td>
<td>5-FU/LV;IRI; OX</td>
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<tr>
<td>Karoui</td>
<td>2006</td>
<td>67</td>
<td>45 (67%)</td>
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<tr>
<td>Vauthey</td>
<td>2006</td>
<td>406</td>
<td>248 (61%)</td>
<td>5-FU/LV;IRI; OX; others</td>
</tr>
<tr>
<td>Aloia</td>
<td>2006</td>
<td>92</td>
<td>75 (82%)</td>
<td>5-FU/LV;OX</td>
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<tr>
<td>Hewes</td>
<td>2007</td>
<td>101</td>
<td>46 (46%)</td>
<td>5-FU/LV;OX</td>
</tr>
<tr>
<td>Sahajpal</td>
<td>2007</td>
<td>95</td>
<td>53 (55%)</td>
<td>5-FU/LV;IRI</td>
</tr>
<tr>
<td>Aloysius</td>
<td>2007</td>
<td>54</td>
<td>54 (100%)</td>
<td>5-FU/LV;OX</td>
</tr>
<tr>
<td>Gomez</td>
<td>2007</td>
<td>386</td>
<td>67 (17%)</td>
<td>5-FU/LV;OX</td>
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<tr>
<td>Pawlik</td>
<td>2007</td>
<td>212</td>
<td>153 (72%)</td>
<td>5-FU/LV;IRI; OX</td>
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<tr>
<td>Mehta</td>
<td>2008</td>
<td>173</td>
<td>130 (75%)</td>
<td>5-FU/LV;OX; others</td>
</tr>
<tr>
<td>Nakano</td>
<td>2008</td>
<td>90</td>
<td>90 (100%)</td>
<td>5-FU/LV;IRI; OX</td>
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<tr>
<td>Kandutsch</td>
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<td>63</td>
<td>47 (71%)</td>
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<td>Scoggins</td>
<td>2009</td>
<td>186</td>
<td>112 (60%)</td>
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<td>Brouquet</td>
<td>2009</td>
<td>146</td>
<td>146 (100%)</td>
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<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Range</td>
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</tr>
</tbody>
</table>

5-FU 5-fluorouracil, LV leucovorin, OX oxaliplatin, IRI irinotecan, NA not available
a Only marked steatosis (≥30% of hepatocytes)
b Steatohepatitis as defined by Kleiner et al.24
c Rubbia-Brand grade 2–3, or unspecified
PERIOPERATIVE OUTCOME AFTER HEPATIC INJURY

Steatosis

The impact of steatosis on perioperative outcome after major hepatectomy for CLM was first examined by Behns et al., who demonstrated increased morbidity and mortality rates depending on the severity of steatosis. However, their results were limited by a small sample size of only 135 patients. Consequently, Belghiti et al. reported increased complication rates after CLM resection when comparing 37 patients with steatosis with 710 with normal livers (22 vs. 8%, \( P = 0.001 \)). Similarly, McCormack et al. found a significantly higher major complication rate of 27% for patients with steatosis (\( n = 58 \)) as compared with 5% for matched controls following major hepatectomy (\( P = 0.001 \)).

Neither study demonstrated a difference in perioperative mortality. The largest study of 485 patients undergoing hepatectomy compared 325 patients with steatotic livers with 160 matched controls. On multivariate analysis, steatosis was found to be an independent predictor of postoperative complications (\( P < 0.01 \)). Overall and infectious complication rates were 62% and 43% for the marked steatosis group (\( n = 102 \)) and 35 and 14% for controls (\( P < 0.01 \)). There was a trend towards increased mortality, although it was not statistically significant. Gomez et al. confirmed these findings of increased infection rates, intensive care unit (ICU) admissions, and biochemical deteriorations in patients with steatosis undergoing hepatic resection for CLM. Multivariate analysis revealed severity of steatosis as an independent predictor of postoperative morbidity (\( P = 0.001 \)).

In summary, current data suggest that moderate to severe steatosis present at time of hepatic resection contributes to increased postoperative morbidity, mostly in the form of infectious complications, but has no clear effect on mortality.

Steatohepatitis

The effects of steatohepatitis on outcome after hepatic resection are less well understood. Fernandez et al. first described an index patient who developed steatohepatitis presumably due to the combined effects of elevated BMI (35 kg/m\(^2\)) and preoperative 5-FU plus oxaliplatin therapy. The multicenter study by Vauthey et al. provides the best outcome data on steatohepatitis to date. This work demonstrated that steatohepatitis induced by irinotecan-based chemotherapy was associated with increased 90-day mortality following major hepatectomy for CLM (14.7 vs. 1.4%, \( P = 0.001 \)). Patients with steatohepatitis also had higher risk of death from postoperative liver failure (6 vs. 1%, \( P = 0.01 \)). In concordance with the two-hit theory for the development of steatohepatitis, the authors found that patients with BMI >25 kg/m\(^2\) were more likely to develop steatohepatitis.

Thus, it seems that steatohepatitis has a detrimental impact on postoperative liver function and patient survival following resection. In the setting of documented or suspected marked steatohepatitis, major hepatectomy should be approached with due caution.

Sinusoidal Obstruction Syndrome (SOS)

Platinum-based drugs are most often associated with SOS, but it remains unclear as to how this condition affects postoperative recovery. Karoui et al. reported significantly higher postoperative morbidity in patients following oxaliplatin-based chemotherapy as compared with controls (38 vs. 14%, \( P = 0.03 \)). This was mostly attributed to higher incidence of transient liver failure in the chemotherapy group (11 vs. 0%). Aloia and colleagues found that patients after oxaliplatin exposure were more likely to receive perioperative blood transfusion (mean 1.9 vs. 0.5 units, \( P = 0.03 \)) and have longer hospital stay (15 vs. 11 days, \( P = 0.02 \)), presumably due to higher incidence of sinusoidal alterations and hemorrhagic centrilobular necrosis in the remnant liver. A trend towards increased mortality was found for patients receiving more than one unit of transfused blood, as previously demonstrated in this patient population. A group from Strasbourg demonstrated significantly impaired functional hepatic reserve in patients with SOS, measured by preoperative indocyanine green retention, which was also associated with higher morbidity (\( P = 0.03 \)) and longer hospital stay (\( P = 0.006 \)) after major hepatectomy compared with patients with normal livers. Recent studies which have evaluated two components of SOS (sinusoidal fibrosis and dilatation) separately, found that fibrosis rather than dilatation was associated with increased intraoperative transfusion requirements and liver failure after hepatectomy for CLM.

Current data illustrate the clinical importance of sinusoidal obstruction syndrome in the setting of hepatic colorectal cancer. The venous obstructive nature of this pathology predisposes to increased blood transfusions and higher morbidity after hepatic resection.

SURGICAL MANAGEMENT OF PATIENTS WITH DAMAGED LIVERS

Effect of Timing and Duration

Although some investigators have demonstrated a negative impact of chemotherapy-associated liver injury on perioperative morbidity as shown above, many studies that directly compare outcomes following hepatic resection for
<table>
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<th>First author</th>
<th>Year</th>
<th>All, n</th>
<th>Majora (%)</th>
<th>Resections</th>
<th>Chemotherapy agents</th>
<th>Median length (months/cycles)</th>
<th>No. of patients</th>
<th>Morbidity (%)</th>
<th>Liver failure (%)</th>
<th>Mortality (%)</th>
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<td>-/11</td>
<td>21</td>
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<td>100</td>
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<td>Vauthay11</td>
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<td>406</td>
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<td>23</td>
<td>18</td>
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<td>-/6</td>
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<td>96</td>
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<td>2008</td>
<td>173</td>
<td>76</td>
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<td>49</td>
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<td>Hubert44</td>
<td>2010</td>
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<td>96</td>
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<td>57</td>
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<td>21–57</td>
<td>12–51</td>
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</table>

S-FU 5-fluorouracil, LV leucovorin, OX oxaliplatin, IRI irinotecan, NS not significant, NA not available

*a Major defined as resection of ≥3 segments
CLM with or without preoperative chemotherapy have not found significant differences (Table 3). A possible explanation for this discrepancy is related to the timing and duration of chemotherapy.

Evidence suggests that proceeding with hepatic resection too soon after discontinuing chemotherapy may be detrimental to liver remnant function. Theoretically, a longer interval may provide the liver time to recover from any reversible hepatotoxic effects of chemotherapy. Welch et al. compared 252 patients who underwent hepatic resection following chemotherapy with 245 patients resected without prior systemic therapy. Overall, more septic (2.4%) and respiratory (10.3%) complications were found in the chemotherapy group as compared with controls (0 and 5.3%, P < 0.003). However, overall complication rates of 11% with a chemotherapy-free interval of <5 weeks decreased by half when surgery was delayed 5–9 weeks after chemotherapy, and fell to under 2.5% following a 9–12-week interval (P = 0.009).

Regarding duration of chemotherapy exposure prior to resection, Karoui et al. reported that patients receiving systemic chemotherapy (mostly oxaliplatin) had a significantly higher rate of sinusoidal dilatation (49 vs. 13.6%, P = 0.005) and postoperative complications (38 vs. 13.5%, P = 0.03) compared with controls. This correlated with the number of chemotherapy cycles administered. Patients who received ≥6 cycles had considerably higher postoperative complications, as compared with those treated with <6 cycles (54 vs. 19%, P = 0.047). Moreover, postoperative liver failure was observed in five patients who received more than ten cycles of chemotherapy.

While the ideal regimen, timing, and duration of chemotherapy are still under investigation, close collaboration between surgical and medical oncologists is necessary to maximize the benefit-to-toxicity ratio and optimize patient selection for preoperative chemotherapy.

Detection of the Impaired Liver

Preoperative biopsy and histologic examination remains the best method to assess toxic liver changes. However, this approach has inherent limitations. Apart from minor concerns of hemorrhage and tumor dissemination, heterogeneity of fat deposition, fibrosis, and inflammation can lead to misrepresentative samples. Furthermore, classification of injuries remains ill defined and often subject to reviewer experience and expertise. Some investigators have advocated staging laparoscopy to visually inspect and sample liver parenchyma prior to performing hepatic resection. This approach, however, may be difficult to apply practically in routine clinical practice. One potential way to standardize classification of preexisting liver injury would be through cross-sectional imaging routinely performed as part of standard preoperative workup.

Steatosis can be detected by computerized tomography (CT), magnetic resonance imaging (MRI), and ultrasonography. Specifically, magnetic resonance spectroscopy has been found to generate reproducible measurements of hepatic triglyceride content. Cho et al. systematically analyzed accuracy of cross-sectional studies in determining steatosis. MRI scored high sensitivity (88%) but low specificity (63%) for estimating the degree of hepatic steatosis. Noncontrast CT was the most reliable method, with excellent sensitivity (100%), but still yielded low specificity (33%) for ruling out steatosis, especially in obese patients.

Further distinction between steatosis and steatohepatitis poses yet another challenge, because intrahepatic inflammation lacks distinctive radiologic appearance. Oliva et al. reported indirect CT features of steatohepatitis, including increased craniocaudal liver span, and an increase in caudate-right lobe ratio. O’Rourke et al. utilized ferucarbotran contrast-enhanced MRI and chemical shift imaging (CSI) MRI. CSI MRI had positive predictive value (PPV) of 100% for chemotherapy-induced steatosis and 80% for steatohepatitis, although neither method reliably distinguished the two. Ferucarbotran-enhanced MRI had PPV of 100% for severe sinusoidal dilatation. Using superparamagnetic iron oxide contrast, radiologists have shown that T2-weighed MRI can effectively detect SOS with sensitivity and specificity of 87 and 89%, respectively.

Despite these advances in radiologic imaging, the gold standard for evaluating toxic liver injury remains through tissue biopsy. Progress continues to be made, especially through refinement in magnetic resonance imaging.

Future Liver Remnant and Portal Vein Embolization

Definition of resectable CLM has evolved from being based upon number of lesions and lobes involved to simply whether or not the future liver remnant (FLR) is compatible with life. A remnant of approximately 20% of original liver volume is generally considered the minimum safe volume for a normally functioning liver, which often translates into the ability to preserve two contiguous segments with adequate arterial and portal venous inflow as well as venous and biliary outflow. However, the presence of underlying liver injury requires larger remnants to support the patient during recovery.

Portal vein embolization (PVE) can promote preoperative compensatory FLR hypertrophy. The average increase of the estimated FLR is 8–16%, occurring within approximately 3–4 weeks following PVE in most cases. Shoup et al. found that FLR of ≤25% total liver volume
more than tripled the risk of postoperative hepatic dysfunction after resection for CLM, which was associated with increased complications and longer hospital stay. Thus, accepted clinical practice has been to perform preoperative PVE if FLR is expected to be ≤30% following extensive chemotherapy, and ≤40% in patients with documented fibrosis or cirrhosis.

A prospective study of 55 patients undergoing right hepatectomy found a mean functional FLR increase of 9% in chronically diseased livers (16% in normal livers) at 4–8 weeks after PVE, which was associated with decreased incidence of postoperative complications and intensive care unit stay. However, PVE has not been shown to improve long-term survival. Based on existing data, it is reasonable to consider PVE prior to major hepatic resection in patients with confirmed or suspected chemotherapy-associated liver injury and estimated FLR ≤30%.

Pedicle Clamping

Hepatic pedicle clamping (Pringle maneuver) is commonly used to interrupt vascular inflow, to reduce bleeding during parenchymal transection. Hepatic outflow occlusion techniques have further been adopted to limit blood loss in extended resections near hepatic veins. While vascular occlusion is well tolerated in patients with otherwise healthy livers, its use in patients with underlying liver disease is less well defined. Animal studies demonstrate that steatotic livers tolerate warm ischemia poorly. The mechanism of ischemia–reperfusion injury was characterized as a shift from an apoptotic cell death in normal livers to necrotic cell death in fatty livers. Extended warm ischemia time may also be associated with increased complication rates, including liver failure and death.

Ischemic preconditioning and intermittent pedicle clamping may actually protect against ischemic liver injury. A prospective trial comparing intermittent portal clamping (IPC) with continuous portal clamping (CPC) found that IPC was better tolerated in patients with abnormal liver parenchyma, as demonstrated by favorable postoperative liver function tests.

Given the limited data, strong recommendations regarding utilization of pedicle clamping cannot be drawn. However, chemotherapy-related liver injuries should be considered when employing intraoperative occlusive vascular techniques in order to minimize perioperative morbidity.

CONCLUSIONS

Preoperative chemotherapy is increasingly being utilized to treat colorectal liver metastases, and has been associated with hepatotoxic changes in resection specimens ranging from mild steatosis to steatohepatitis and sinusoidal obstruction syndrome. Studies have shown that patients with damaged livers have higher perioperative morbidity and mortality as compared with patients with healthy livers.

While presence of steatosis has been linked to increased postoperative complications, mostly infectious in nature, more severe forms of injury such as steatohepatitis have been associated with increased postoperative mortality. Venous-occlusive disorders, often seen after platinum-based chemotherapy, may predispose to higher perioperative transfusion requirements and increased morbidity.

Several recent studies, which have compared perioperative outcomes in patients with and without preoperative chemotherapy, have not been able to demonstrate this phenomenon. Extensive duration of preoperative chemotherapy and short time interval between its cessation and surgery may predispose to increased perioperative complications. Evolving imaging techniques, especially advances in magnetic resonance imaging, offer promise towards noninvasive detection of underlying liver disease. Preoperative assessment of liver damage and identification of high-risk patients, along with techniques such as PVE and intermittent pedicle clamping, may serve to minimize postoperative morbidity in patients undergoing resection of hepatic colorectal cancer metastases.

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