Hepatic Toxicities Associated with the Use of Preoperative Systemic Therapy in Patients with Metastatic Colorectal Adenocarcinoma to the Liver

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ABSTRACT

Colorectal cancer patients with isolated liver metastasis are potentially cured with surgical resection. Recent advances in systemic chemotherapy have increased the ability to convert unresectable metastatic liver lesions to resectable lesions. The cost in toxicity of these therapeutic advances is increasingly being recognized. Numerous reports have demonstrated an association between irinotecan and steatohepatitis as well as between oxaliplatin and sinusoidal dilation. In this review, we summarize the current clinical experience with these hepatic toxicities and discuss the role they play in determining postoperative morbidity. We also review emerging safety data regarding the use of bevacizumab and cetuximab. Finally, we give specific clinical examples of how multidisciplinary teams can best manage patients receiving preoperative chemotherapy for potentially resectable liver metastases.

INTRODUCTION

Of the almost 150,000 cases of colorectal adenocarcinoma diagnosed each year, close to one third of them have liver metastases either at the time of diagnosis or during the disease course. The well-known track record for surgical resection of metastatic liver lesions coupled with the development of more active systemic chemotherapy and biologic regimens have made multidisciplinary treatment the mainstay of the treatment strategy for metastatic colorectal cancer to the liver [1, 2]. With the increasing use of systemic therapy, we have witnessed the impressive tumor response data that have improved resectability in some patients [3–5]. At the same time, we are beginning to appreciate the wide spectrum of hepatic toxicities associated with the use of various systemic agents and regimens. In this review we attempt to summarize the current experience...
with the hepatic toxicity of different chemotherapeutic and biologic agents.

There are at least four categories of patients with metastatic colorectal cancer to the liver. First, the hepatic lesion(s) are clearly resectable at the time of presentation. Second, the hepatic lesion(s) are potentially resectable but this may require careful planning, including portal vein embolization to increase the hepatic reserve, staged resection, or combination with radiofrequency ablation. Third, the hepatic lesion(s) are unresectable at presentation but potentially convertible to resection after administering preoperative chemotherapy, which we refer to as conversion chemotherapy. In general, the term neoadjuvant is used when the treatment is given preoperatively, adjuvant when the treatment is given postoperatively, and perioperative when the treatment is given both before and after surgery. Fourth, the hepatic lesion(s) are unresectable and unlikely to be convertible even with effective systemic therapy.

The strategy of giving conversion chemotherapy is widely accepted [6, 7]. A major goal of conversion chemotherapy is decreasing the tumor size and burden sufficiently so that unresectable patients can become candidates for surgery. Adam et al. [3] published an important surgical series demonstrating the feasibility of this approach. Their series examined 1,104 patients who were initially deemed unresectable [3]. Following chemotherapy, 138 (12.5%) of these patients had enough shrinkage of their tumor to be considered resectable. The survival of the patients resected after conversion chemotherapy, although not as good as patients who went directly to surgery, was still impressive. Specifically, the 5-year survival rate of patients following conversion chemotherapy was 33%, whereas the 5-year survival rate of patients who went directly to surgery was 48% [3].

Besides the potential to downsize a tumor, conversion chemotherapy also provides a window of time to observe the biological behavior of a tumor. This has great practical importance because it can prevent unnecessary hepatectomies in patients who rapidly develop metastatic disease either within or outside their liver. In addition, the response to preoperative chemotherapy provides important information about drug sensitivity and the rationale for selecting a postoperative treatment regimen. Moreover, the response to preoperative chemotherapy may predict the overall prognosis, as demonstrated recently by Blazer and colleagues [8].

**Types of Hepatotoxicity Caused by Chemotherapy**

Although preoperative chemotherapy has many advantages, there has been growing concern about the potential for hepatotoxicity [9, 10]. This concern is buttressed by pathological observations of livers from patients who received preoperative chemotherapy. The types of pathology observed in liver specimens from patients treated with preoperative chemotherapy include steatosis, steatohepatitis, and sinusoidal injuries (Figure 1).

Steatosis refers to the accumulation of lipids within the hepatocyte [11]. The mechanism leading to this lipid accumulation is unclear. The liver is an important site in the production of lipoproteins [such as low density lipoprotein (LDL)] and is a major glycogen storage site. Dysregulation of either of these processes could lead to lipid accumulation. Other possible mechanisms include disruption of the mitochondria, leading to increased oxidation of cellular proteins.

Steatosis is considered an early stage of nonalcoholic fatty liver disease [12]. In later stages of this disease, steatosis is accompanied by an inflammatory response. This inflammation leads to fibrosis and is termed steatohepatitis. Steatohepatitis can lead to significant decreases in liver function. Nonalcoholic steatohepatitis (NASH) is a condition seen in patients with obesity and diabetes. The clinical course of patients with NASH is highly variable. Over a 10-year period, approximately 9%–20% of patients with NASH develop cirrhosis [13]. Of the patients who develop cirrhosis, 22%–33% of them develop end-stage liver disease [13].

One of the difficulties in analyzing steatosis and steatohepatitis is that they are very prevalent conditions. Published reports of the prevalence of steatosis ranges from a 16.4% incidence in Northern Italy to a 31% incidence in the U.S. [14, 15]. Interestingly, because of greater alcohol use and obesity, the rates of steatosis are consistently higher in men than in women. In the Northern Italy series, the prevalence of steatosis in patients who heavily consumed alcohol was 46%, and in obese patients (body mass index $>30$ kg/m$^2$) it was as high as 75% [14].

Whereas steatosis and steatohepatitis directly interfere with the function of hepatocytes, sinusoidal obstruction syndrome results from damage to endothelial cells lining the sinusoids of the liver [16, 17]. Sinusoidal obstruction syndrome was previously termed veno-occlusive disease. Veno-occlusive disease is a well-known complication of the high-dose chemotherapy regimens used in stem cell transplantation. Sinusoidal obstruction syndrome can lead to portal hypertension, ascites, hyperbilirubinemia, and in severe cases, liver failure. One of the hallmarks of sinusoidal obstruction syndrome is sinusoidal dilation.

For the remainder of this review, we discuss the correlation among chemotherapeutic agents, specific liver pathologies, and adverse postoperative outcomes. One of the challenges in reviewing this information is that there are...
differences in the definitions of specific pathologies and postoperative events. For example, pathologists sometimes disagree about the distinction between steatosis and steatohepatitis. In addition, some papers only report all cases of sinusoidal dilation, whereas other report only severe cases of sinusoidal dilation. Furthermore, operative mortality is also reported differently. Some authors report only 30-day mortality figures, whereas other papers report mortality figures over longer time intervals from surgery. These differences likely account for the heterogeneity and differing conclusions of the studies discussed below.

**CHEMOTHERAPY AND STEATOsis**

5-Fluorouracil (5-FU) is the backbone of most first-line chemotherapy regimens used for preoperative chemotherapy. Prior to 2000, standard treatment for metastatic colorectal cancer was single-agent 5-FU combined with leucovorin. The response rate with 5-FU and leucovorin is approximately 20% [18]. Modern chemotherapy regimens have substantially improved these results by combining 5-FU and leucovorin with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). These modern regimens show higher response rates of approximately 50% [19–24].

An association between steatosis and chemotherapy was first discovered by several pathological and radiological studies on patients who received 5-FU. All the reported studies observed a high incidence of steatosis. For example, using computed tomography (CT) scan screening before and after chemotherapy, Peppercorn et al. [25] observed that 47% of patients treated with six to 12 cycles of 5-FU...
developed steatosis. More recently, it has become appreciated that all the chemotherapy agents used in colorectal cancer appear capable of causing steatosis. This was demonstrated by Vauthey et al. [26], who observed no differences in the rates of steatosis among different chemotherapy regimens.

Several case series within the surgical literature have examined whether steatosis increases surgical morbidity. The first published report was from the Mayo Clinic. That paper, which examined 135 patients receiving liver surgery in 1990–1993, showed that moderate to severe steatosis is associated with greater perioperative mortality [27]. In that case series, patients with steatosis had greater morbidity, with higher rates of postoperative liver failure and biliary leakage. McCormack et al. [28] also observed greater postoperative morbidity in patients with steatosis and noted a nonstatistically significant trend toward higher mortality. Other surgical series did not observe any difference in mortality but did observe greater morbidity. Specifically, Belgiti et al. [29] compared 37 patients with steatosis with 478 controls and found that the patients with steatosis had greater postoperative morbidity. Furthermore, surgical series from Kooby et al. [30] and Gomez et al. [31] both showed that patients with severe steatosis had more postoperative liver dysfunction, infectious complications, and time spent in the intensive care unit.

**IRINOTECAN AND STEATOHEPATITIS**

Steatohepatitis was first noted as a complication of chemotherapy in a small surgical series from the University of Washington [32]. In that series, the authors observed a higher rate of steatohepatitis in 14 patients treated with irinotecan or oxaliplatin [32]. Importantly, 12 of the 14 patients received irinotecan (10 of those received only irinotecan and two received both irinotecan and oxaliplatin).

The association between irinotecan and steatohepatitis was clearly demonstrated by Vauthey et al. [26]. They examined a series of 94 patients treated with FOLFIRI. Strikingly, they observed that 20% of those patients developed steatohepatitis. Similar findings were reported by Pawlik et al. [33]. Of note, Vauthey et al. [26] found that obese patients had a higher risk for developing irinotecan-induced steatohepatitis. A trend toward a higher risk for steatohepatitis in obese patients treated with irinotecan was also observed by Fernandez et al. [32] and Pawlik et al. [33] (Table 1).

The higher rate of steatohepatitis caused by irinotecan appears to have clinically relevant consequences. Vauthey et al. [26] found that patients with steatohepatitis had a significantly higher 90-day mortality rate than patients without steatohepatitis (14.7% versus 1.6%). In that series, patients with steatohepatitis had a higher risk for developing end-stage liver failure that led to death. However, it should be noted that two smaller surgical series did not show a difference in morbidity or mortality in patients treated preoperatively with irinotecan-containing regimens [33, 34]. This may simply reflect the variability in diagnosing and grading steatosis and steatohepatitis.

**OXALIPLATIN AND SINUSOIDAL DILATION**

Unlike irinotecan and 5-FU, oxaliplatin’s major liver toxicity appears to be directed against the endothelial cells lining the sinusoids. A group from Switzerland was the first to observe that patients treated with oxaliplatin developed abnormalities within their hepatic sinusoids [35]. In their retrospective case study, Rubbia-Brandt et al. [35] found that 34 of 43 (78%) patients treated with oxaliplatin developed sinusoidal dilation. Multiple other surgical series support this observation. For example, a recent surgical series from Mehta et al. [36] demonstrated that 52.8% of the 70 patients receiving regimens containing oxaliplatin developed sinusoidal dilation. Three other studies found that 9.7%–23% of patients treated with oxaliplatin developed grade 2–3 sinusoidal dilation [26, 33, 37] (Table 2).

Ongoing analysis has shown that oxaliplatin is associ-

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**Table 1. Summary of case series reporting an association between irinotecan and steatohepatitis**

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Chemotherapy</th>
<th>Steatohepatitis</th>
<th>Greater mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vauthey et al. [26]</td>
<td>94</td>
<td>Irinotecan, 94</td>
<td>19 of 94 patients (20%)</td>
<td>Yes*</td>
</tr>
<tr>
<td>Pawlik et al. [33]</td>
<td>55</td>
<td>Irinotecan, 55</td>
<td>2 of 55 patients (4%)</td>
<td>No</td>
</tr>
<tr>
<td>Fernandez et al. [32]</td>
<td>14</td>
<td>Irinotecan, oxaliplatin, oxaliplatin</td>
<td>4 of 14 patients (28%)</td>
<td>NA</td>
</tr>
<tr>
<td>Sahajpal et al. [34]</td>
<td>9</td>
<td>Irinotecan, 9</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>

*Vauthey et al. [26] found greater postoperative mortality in patients with steatohepatitis.

Abbreviation: NA, not available.
ated with a broader pattern of parenchymal hepatic injury, including nodular regenerative hyperplasia, peliosis, and centrilocular vein fibrosis [38]. The clinical implications of these complications remain to be fully evaluated.

An area of controversy is whether oxaliplatin increases perioperative morbidity following hepatectomy. The strongest evidence that oxaliplatin increases surgical morbidity comes from a large randomized trial, the European Organization for Research and Treatment of Cancer (EORTC) Intergroup trial 40983, which compared surgical resection alone with perioperative (i.e., chemotherapy before and after surgery) FOLFOX4 chemotherapy [39]. In that trial, 25% of 182 patients receiving FOLFOX4 chemotherapy had reversible complications, compared with only 16% of the patients in the surgery-only group \((p = .04)\). Notable complications experienced by patients in the perioperative chemotherapy arm included liver failure, biliary fistula formation, and intra-abdominal infection. Importantly, although morbidity was greater, there was no difference in mortality between the two groups.

The observation that oxaliplatin increases surgical morbidity but not mortality is supported by two other surgical series. Aloia et al. [40] compared patients treated with preoperative chemotherapy with those who did not receive chemotherapy. Their series was heavily weighted toward patients taking oxaliplatin (in their series 23 patients received 5-FU plus leucovorin and 52 patients received FOLFOX). They found that patients treated with preoperative chemotherapy tended to have a higher rate of morbidity than patients who were not treated with chemotherapy. They further demonstrated that patients treated with preoperative chemotherapy required greater amounts of blood transfusions. Upon further analysis, a strong correlation was noted between patients requiring large amounts of blood transfusions and vascular injury in the liver. Of note, in their large retrospective analysis, Welsh et al. [41] also noted that patients treated with preoperative oxaliplatin-containing regimens had higher rates of intraoperative bleeding.

The findings of Nakano et al. [42] also support the idea that oxaliplatin-induced sinusoidal damage increases postoperative morbidity. In their case series of 90 patients treated with preoperative chemotherapy, they found that patients with sinusoidal injury had higher rates of postoperative complications and longer hospital stays. Complications observed in patients with sinusoidal injury by Nakano et al. [42] included liver failure and the formation of a biliary fistula.

While the findings of Aloia et al. [40], Nakano et al. [42], and the EORTC Intergroup trial 40983 suggest that oxaliplatin increases morbidity from hepatectomy, several other case series show no difference in morbidity or mortality. Specifically, the M.D. Anderson Cancer Center, Johns Hopkins, England, and Vienna groups reported that there was no significant difference in postoperative mortality and morbidity in patients receiving oxaliplatin [26, 33, 36, 37]. Mehta et al. [36] did note a nonstatistically significant trend toward more biliary complications in patients receiving oxaliplatin.

Finally, some authors have suggested that regimens containing 5-FU, irinotecan, and oxaliplatin (FOLFOXIRI) could have greater efficacy in downstaging unresectable patients. The obvious concern about FOLFOXIRI is that it could lead to greater toxicity. Masi et al. [43] reported a pooled analysis of three phase II/III clinical trials that gave patients FOLFOXIRI. Interestingly, they found that patients treated with FOLFOXIRI had a 70% response rate. Furthermore, they found that 25 of the 73 patients (34%) with initially unresectable liver metastases were able to receive a hepatectomy with curative intent. There was no postoperative mortality in the 25 patients who received the hepatectomy. Although 27% of the patients suffered post-

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Table 2. Summary of case series reporting an association between oxaliplatin and sinusoidal dilation

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Sinusoidal dilation</th>
<th>Greater morbidity</th>
<th>Greater mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vauthey et al. [26]</td>
<td>79</td>
<td>15 of 79 patients (19%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mehta et al. [36]</td>
<td>70</td>
<td>43 of 70 patients (61%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Aloia et al. [40]</td>
<td>52</td>
<td>10 of 52 patients (19%)</td>
<td>Yes(^a)</td>
<td>No</td>
</tr>
<tr>
<td>Kandutsch et al. [37]</td>
<td>47</td>
<td>11 of 47 patients (23%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rubbia-Brandt et al. [35]</td>
<td>43</td>
<td>34 of 43 patients (78%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pawlik et al. [33]</td>
<td>31</td>
<td>3 of 31 patients (10%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nakano et al. [42]</td>
<td>90</td>
<td>38 of 90 patients (42%)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^a\)Aloia et al. found a non–statistically significant trend toward increased morbidity.

Abbreviation: NA, not available.
operative complications, these complications “resolved without sequelae.” In terms of pathological changes, one patient was found to have steatohepatitis, and sinusoidal dilation was noted in 100% of the patients. Importantly, the sinusoidal dilation was relatively mild and none of the patients had grade III/IV sinusoidal dilation.

**BEVACIZUMAB**

Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). It is an angiogenesis inhibitor that was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer in 2004 [44]. In multiple randomized clinical trials, when added to FOLFOX and FOLFIRI, bevacizumab led to greater response rates and survival times in metastatic colorectal cancer patients [45–48]. Bevacizumab also appears to be effective in the preoperative setting. In a study from M.D. Anderson Cancer Center, patients treated with FOLFOX plus bevacizumab had fewer viable cancer cells within their liver metastases than patients treated with FOLFOX alone [49].

Data are beginning to emerge on the safety of hepatectomy in patients treated with preoperative regimens containing bevacizumab (Table 3). These data have been greatly anticipated because of concerns about bleeding and wound healing following surgery. Furthermore, clinical studies have clearly demonstrated that surgery of any kind while on bevacizumab impairs wound healing. Specifically, a pooled analysis of two large clinical trials showed that patients who needed surgery of any kind while being treated with bevacizumab had a higher rate (13% versus 3.4%) of grade III/IV wound-healing complications than patients treated with placebo [50].

The M.D. Anderson Cancer Center group published a surgical series analyzing the safety of preoperative regimens containing bevacizumab (Table 3). Their series compared 81 patients who received preoperative regimens containing bevacizumab with 44 patients who received chemotherapy alone. There was no difference in morbidity or mortality between the two groups. These data are in agreement with a surgical series of 39 patients treated with bevacizumab combined with chemotherapy at Duke Comprehensive Cancer Center and another smaller series published by researchers at the Memorial Sloan-Kettering Cancer Center [52, 53]. Finally, a recent single-arm phase II clinical trial demonstrated that patients who received capecitabine and oxaliplatin plus bevacizumab tolerated hepatectomy well [54]. The authors found that the rate of complications was equivalent to that of historical controls of patients treated with preoperative chemotherapy.

![Table 3. Summary of case studies reporting on the safety of bevacizumab](http://theoncologist.alphamedpress.org/)

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Greater morbidity</th>
<th>Greater mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kesmodel et al. [51]</td>
<td>81</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Reddy et al. [53]</td>
<td>39</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>D’Angelica et al. [52]</td>
<td>32</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Patients in the D’Angelica et al. [52] case series received perioperative bevacizumab.

Despite these encouraging findings, other reports have raised concerns about regeneration of the liver after bevacizumab treatment. Preclinical studies have suggested that VEGF receptor inhibition can adversely affect murine liver regeneration [55, 56]. At the clinical level, Aussilhou et al. [57] recently found less liver hypertrophy following portal vein embolization (PVE) in 13 patients treated with FOLFOX or FOLFIRI plus bevacizumab compared with 27 patients treated with FOLFOX or FOLFIRI without bevacizumab. The amount of liver hypertrophy was significantly less in patients treated with longer durations of bevacizumab-containing chemotherapy regimens. Patients treated with fewer than six cycles of bevacizumab had substantially more liver hypertrophy following PVE than patients treated with more than six cycles of bevacizumab [57]. It should be noted that 10 of the 13 patients were treated with more than six cycles of FOLFOX or FOLFIRI plus bevacizumab. Given that patients in that series received relatively large amounts of chemotherapy, it is possible that the decreased amount of liver hypertrophy following PVE was precipitated by the chemotherapy agents administered with bevacizumab [58].

Unexpectedly, data are emerging that suggest that bevacizumab may protect against sinusoidal damage. This protective benefit of bevacizumab was first seen by Ribero et al. [49] when they compared 62 patients treated with FOLFOX plus bevacizumab with 43 patients treated with FOLFOX alone. They found that the FOLFOX plus bevacizumab–treated patients had a lower severity of sinusoidal injury [49]. In agreement with this, Klinger et al. [54] also found a statistically significant lower rate of severe sinusoidal dilation in patients given FOLFOX plus bevacizumab. They found that only 1.9% of the patients treated with FOLFOX plus bevacizumab had high-grade (grade 3) sinusoidal dilation, compared with 23.9% of the patients treated with FOLFOX alone [54]. However, to date there is no indication if severe parenchymal lesions associated with oxaliplatin, like nodular regenerative hyperplasia and sinusoidal obstruction syndrome lesions, are reversible with bevacizumab.
An important consideration, because of concerns about bleeding and wound healing, is how long bevacizumab should be stopped prior to surgery. Adding to this concern is the fact that bevacizumab is slowly cleared from the body and has a median half-life of 20 days. The M.D. Anderson Cancer Center group found that the time interval between bevacizumab and surgery did not influence the complication rate [51]. In their series, the last dose of bevacizumab was given 31–117 days prior to surgery. On the other hand, the group from Duke Comprehensive Cancer Center did note that there was a trend, although not statistically significant, toward more hepatic complications when bevacizumab was given <8 weeks prior to therapy [53].

CETUXIMAB
Cetuximab (Erbitux®; Bristol-Myers Squibb, New York) is a chimeric monoclonal antibody that targets the epidermal growth factor receptor (EGFR). Like bevacizumab, cetuximab was approved by the U.S. FDA for the treatment of metastatic colorectal cancer in 2004 [59, 60]. A major advance in colorectal cancer treatment was the recent demonstration that cetuximab is primarily effective only in patients with K-Ras wild-type tumors. Remarkably, the Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) study demonstrated that the response rate for FOLFIRI plus cetuximab was 59% in patients with K-Ras wild-type tumors [61].

Preclinical data are mixed regarding the effect of EGFR inhibition on hepatic regeneration. Whereas one report showed strong genetic evidence that EGFR is essential in hepatic regeneration, another report showed that cetuximab administration does not adversely affect hepatectomized mice [55, 62].

There are relatively little clinical data available regarding the safety of administering cetuximab prior to hepatectomy. Adam et al. [63] published a surgical case series in which patients with initially chemotherapy-resistant tumors were given cetuximab-containing chemotherapy regimens. Impressively, 27 of the 151 initially chemotherapy-resistant patients had a downstaging in response to the cetuximab combination chemotherapy. In terms of complications, one of the 27 patients died from liver failure following a repeat major hepatectomy within 60 days of the initial surgery. The overall complication rate was 50% and included two biliary leaks, three infected collections, and two cases of liver insufficiency. Of note, after a median of 16 months of follow-up, 92% of the patients who underwent resection were alive and 40% of those patients were disease free.

OPTIMUM DURATION AND TIMING OF GIVING SYSTEMIC THERAPY
An important question for both medical and surgical oncologists is determining the optimal number of cycles of preoperative chemotherapy. Unfortunately, the data addressing this question are relatively sparse. Alioa et al. [40] found that patients who received >12 cycles of chemotherapy had higher rates of complications and longer postoperative hospitalizations. This is also supported by the finding of Karoui et al. [64] that postoperative morbidity was strongly correlated with more cycles of chemotherapy. Furthermore, Masi et al. [43] argued that the reason the patients in their clinical trial tolerated hepatectomy following FOLFOXIRI is that they received a relatively modest amount (median, 11 cycles) of chemotherapy.

Even fewer data are available regarding the optimal interval between the completion of chemotherapy and surgery. In their retrospective analysis, Brouquet et al. [65] found higher rates of “chemotherapy associated liver injury” (patients with >30% steatosis, steatohepatitis, or moderate to severe sinusoidal dilation) in patients operated on ≤4 weeks after completing chemotherapy. Similar findings were observed by Welsh et al. [41] in a large retrospective study of 750 patients. They found that the rate of surgical complications was lower with longer intervals between chemotherapy completion and surgery. Specifically, they found that patients operated on ≤4 weeks after chemotherapy had an 11% rate of complications, whereas the rate of surgical complications was 5.5% 5–8 weeks after chemotherapy and 2.6% 9–12 weeks after chemotherapy.

PREOPERATIVE ASSESSMENT OF RISK FOR HEPATIC TOXICITY
Preoperative assessment for significant liver pathology is a challenging clinical problem with the currently available tools. Although laboratory testing is an essential part of the preoperative workup, the sensitivity of liver function testing is poor. While abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values may be a tip-off, patients with steatohepatitis and sinusoidal dilation can have normal liver function tests. Demonstrating this, Kunde et al. [66] found that the sensitivity of an abnormal serum ALT level to predict NASH was 42% [66, 67].

The accuracy of radiological assessment of liver pathology significantly constrains the ability to risk stratify patients prior to hepatectomy. The sensitivity of ultrasound in detecting steatosis is 60%–94% and the specificity is 66%–95% [68]. Park et al. [69] found that the sensitivity of non-enhanced CT scans was 82% and the specificity was 100% [68, 69]. Unfortunately, although imaging techniques are relatively good at detecting steatosis, they have not been

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proven to be useful in the detection of steatohepatitis and sinusoidal dilation. However, a recent study increases optimism that emerging magnetic resonance imaging (MRI) technologies may one day have more clinical impact. That blinded study examined the ability of chemical-shift imaging (CSI)-MRI and ferucarbotran-enhanced MRI to predict chemotherapy-induced liver injury in 37 patients [70]. It found that CSI-MRI diagnosed steatosis and steatohepatitis with high specificity. Likewise, ferucarbotran-enhanced MRI diagnosed moderate–severe sinusoidal dilation with high specificity.

Preoperative liver biopsies have also been proposed as a way of enhancing patient selection. Opinions are mixed about whether these biopsies can be helpful. Detractors point out that liver biopsies are not benign procedures and tissue obtained from the biopsy is not necessarily representative of the entire liver. Belghiti and Ogata [71] recommend that biopsy of normal liver parenchyma be performed in patients with markedly elevated liver function tests or evidence of significant steatosis on imaging studies.

Another approach that some centers have advocated is performing a laparoscopy prior to doing the hepatectomy [26]. Others have suggested that PVE be used to screen patients for surgery [10, 72]. They argue that the degree of hepatic hypertrophy following PVE is an excellent functional assessment of the liver. Ribero et al. [73] recommended that patients whose livers are unable to hypertrophy in response to PVE should be excluded from undergoing a hepatectomy.

**SUMMARY AND CONCLUSIONS**

Over the past decade, our awareness of the potential hepatic toxicities of preoperative chemotherapy has dramatically increased. Although there are still many unanswered questions, a consensus can be reached regarding some important issues. The associations between chemotherapy and steatosis, irinotecan and steatohepatitis, and oxaliplatin and sinusoidal injury have been clearly established (Table 4). We also feel that the data, when taken as a whole, strongly suggest that preoperative chemotherapy regimens containing irinotecan or oxaliplatin lead to greater postoperative morbidity. Significantly, neither irinotecan- nor oxaliplatin-containing regimens appear to lead to greater postoperative mortality.

In regard to biological therapy, data are beginning to emerge on the safety of bevacizumab and cetuximab. More data are currently available regarding the safety of bevacizumab. Although more research is clearly needed, the data reported thus far suggest that the addition of bevacizumab to preoperative chemotherapy regimens does not increase surgical morbidity. An important unanswered question about bevacizumab is how long it needs to be stopped prior to surgery. Until more data are collected, we feel it is prudent to stop bevacizumab 6–8 weeks prior to surgery. In regard to cetuximab, more data are needed before making any conclusions on its safety.

It is essential that medical and surgical oncologists closely collaborate on colorectal cancer patients with isolated liver metastasis. In light of the potential toxicity of chemotherapy, it is imperative to minimize the amount of preoperative chemotherapy. However, the reason multidisciplinary collaboration is essential is that each case should be approached on an individualized basis. In most cases, bringing patients to surgery as soon as they become resectable is appropriate. Consider, for example, a patient who presents with liver metastasis that could potentially be converted from unresectable to resectable. The goal in this situation should be treating with chemotherapy until resectability rather than to best response. A corollary to this is the scenario in which a patient previously treated with chemotherapy develops a resectable liver metastasis months after completing therapy. This patient also should be taken directly to surgery without further chemotherapy.

On the other hand, in some cases it is appropriate to give preoperative therapy to chemotherapy-naïve patients with resectable tumors. For example, patients who initially present with synchronous but resectable liver metastasis could benefit from the prognostic information derived while undergoing chemotherapy. Delaying surgery allows the multidisciplinary team time to observe the biological behavior of the cancer and see if additional metastatic lesions develop. Furthermore, surgical input is essential in patients who initially present with resectable lesions because surgeons can assess whether shrinkage with chemotherapy could reduce the extent of the hepatic resection. This is important because in some cases downsizing with chemotherapy can drastically reduce the extent of an oper-
ation and allow a significant volume of the liver to be spared.

It is important to note that the vast majority of data covered in this review are from retrospective surgical and pathological series. These case series are published by institutions that have vast experience in performing hepatectomies. Hence, because of patient selection and surgical expertise, we feel it is likely that their data underestimate the rate of complications that would occur at less experienced hospitals.

New strategies are needed to minimize the postoperative morbidity caused by irinotecan and oxaliplatin. One potential way of minimizing complications would be the use of pharmaceutical agents that could counteract the damage from chemotherapy. For example, recent studies of NASH patients suggest that atorvastatin (Lipitor®; Pfizer Inc., New York) may decrease the severity of steatohepatitis [74]. In addition to this, Brouquet et al [65], found that aspirin decreased the rate of chemotherapy-induced sinusoidal lesions.

In conclusion, advances in chemotherapeutic and biological therapies have increased our ability to convert patients with metastatic colorectal cancers to the liver from unresectable to resectable. These therapeutic advances are not without cost and it is important to be mindful of their potential toxicities. The best practice is for multidisciplinary teams to carefully plan and monitor each individual patient’s chemotherapeutic regimens. In this way, the amount of chemotherapy can be optimized so that the patient derives the most potential benefit while suffering the least possible toxicity. Finally, great caution should be used in patients at risk for NASH. Specifically, careful thought should be given to hepatectomy in obese, diabetic, and alcoholic patients who received preoperative chemotherapy.

REFERENCES


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