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Chapter 17

The Assessment and Management of Chemotherapy Associated Liver Injury

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Additional information is available at the end of the chapter

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1. Introduction

Historically chemotherapy for the treatment of colorectal cancer consisted of the thymidylate synthase inhibitor 5-FU (Adrucil®, Fluouracil®, Efudex®, Fluoroplex®), or more recently it's oral pro-drug Capecitabine (Xeloda®), in combination with Folinic acid. Alone these agents were associated with overall tumour response rates in the order of 20%.[10] In the last decade newer agents such as Oxaliplatin and Irinotecan have emerged on the market. These agents are not administered alone but normally in combination with a thymidylate synthase inhibitor. These combinations have seen the reported objective response to chemotherapy rise to typical rates of 50%.[11-13]

In parallel with the development of these conventional chemotherapeutics a new class of biological agents, i.e. antibody based therapies, have emerged. These agents are used to tackle specific pathways in tumour growth and development such as angiogenesis (e.g. anti-VEGFA antibody Bevacizumab) or cellular proliferation (e.g. the anti-epidermal growth factor antibodies Cetuximab and Panitumumab). When these agents are added to Oxaliplatin or Irinotecan based chemotherapy a further 10-15% increase in overall tumour response rate can be obtained.[14-17]

This improvement in response rates has led to a resurgence of interest in utilising chemotherapy as a means of down-sizing metastatic disease to enable subsequent surgical resection – so called conversion chemotherapy.[18] This approach was initially described in 1996 in a series of 330 patients with inoperable colorectal liver metastases of whom 53 (16%) were able to undergo a subsequent liver resection with curative intent after receiving systemic chemotherapy. The five year survival for these patients was 40% which compared favourably to patients with operable disease treated with surgery alone during the same period.[19] In 2004 the same group reported the outcome of 1104 patients with initially unresectable col-

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orectal liver metastases who were treated primarily with systemic chemotherapy over an 11 year period from 1988 – 1999. Of this cohort 138 patients had a sufficient response to chemotherapy to permit subsequent curative intent surgery with an overall 5 year survival of 33% being achieved.[20]

In a small phase II trial of 42 patients with inoperable colorectal liver metastases Alberts et al reported that systemic treatment with 5-FU/Oxaliplatin was associated with a tumour response rate of around 60% with 14 patients (33%) having a sufficient response to permit a liver resection with curative intent.[21] Similar results have been reported with a 5-FU/Irinotecan regimen by Nuzzo et al with 15 out of 42 patients (36%) with inoperable disease being able to undergo subsequent surgical treatment.[22] In an attempt to determine the most appropriate regimen for use as conversion chemotherapy the GERCOR trial randomised patients with inoperable metastatic colorectal cancer to receive either 5-FU/Irinotecan until disease progression or unacceptable toxicity and then 5-FU/Oxaliplatin or the reverse sequence (n=113 per arm). Those patients receiving first line Oxaliplatin demonstrated a higher resection rate (n=24; 22%) than those receiving first line Irinotecan (n=10; 9%) and as such this is the approach most commonly applied in UK practice.[23]

More recently studies have been designed to determine the role of the biological agents in conversion therapy. In the phase II uncontrolled BOXER trial 46 patients with inoperable colorectal liver metastases were treated with Capecitabine/Oxaliplatin in combination with Bevacizumab. 35 of these patients experienced an objective tumour response with 18 (40%) able to undergo a liver resection with curative intent. In addition 5 patients (11%) experienced a complete radiological response to systemic therapy.[24] The CRYSTAL trial randomised patients with inoperable metastatic disease to Irinotecan/5-FU either alone or in combination with Cetuximab and found that the addition of Cetuxmiab was more likely to result in patients undergoing subsequent R0 liver resection with curative intent (Odds Ratio 3.02; p=0.002).[17] It is important to note that the response to Cetuximab is primarily determined by KRAS mutation status. In the Crystal trial there was no evidence of benefit in patients with mutant KRAS who received Cetuximab as compared to those who received 5-FU/Irinotecan alone.[25]

For those patients who receive successful conversion chemotherapy and are subsequently considered for liver resection with curative intent it is important to be aware of what the likely long term outcome will be. Adam et al. reported a series of 184 patients with initially inoperable disease who underwent hepatectomy after systemic therapy. In these patients a 5 year overall survival rate of 33% was obtained although it is important to note that a significant proportion of patients in this study underwent 2 or more surgical procedures, often interspersed with further chemotherapy, before long lasting disease control was obtained.[26]

Whilst the role of conversion chemotherapy is widely accepted in the HPB community more recently the question has been asked about what role systemic therapy may play in the management of patients presenting with operable disease from the outset i.e. true neoadjuvant chemotherapy. The EPOC trial was a multicentre randomised controlled trial which allocated such patients to receive either surgery alone or 6 cycles of 5-FU/Oxaliplatin prior to surgery followed by a further 6 cycles of therapy after surgery (n=182 per arm). Of those

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patients randomised just over 80% of patients in both arms underwent a curative intent liver resection. When the results of this study were analysed on an intention to treat basis there was a non-significant trend to improved 3 year overall survival in the chemotherapy arm (35.4% vs. 28.1%; p=0.058) although statistical significance was only achieved when the analysis was limited to only those who underwent resection (42.4% vs. 33.2%; p=0.025).[27] The difficulty in interpretation of the EPOC trial is that it is impossible to know whether the benefits of peri-operative chemotherapy were primarily a result of the neoadjuvant or adjuvant treatment or if both are required. This important question remains, at present, unanswered.

At present most authors would agree that there is insufficient evidence to consider all patients with operable disease candidates for systemic therapy prior to surgery although it may play a role in those with poor prognostic features such as multiple tumour deposits, a large tumour size or extra-hepatic disease.[28, 29] What is clear however is that an ever increasing number of patients are presenting for surgical resection on the background of multiple cycles of chemotherapy.[30] As experience of managing this patient cohort has increased there has been a growing recognition that the use of chemotherapy can be associated with a toxic injury to the liver parenchyma.[31] The nature of this liver injury and its implication for the surgical approach to these patients will form the subject of the remainder of this chapter.

2. Chemotherapy associated liver injury

2.1. Steatosis/steatohepatitis

The presence of fatty change within the liver is increasingly prevalent in the general adult population where it is commonly associated with the presence of obesity and insulin resistance (i.e. the metabolic syndrome). Fatty liver disease represents a spectrum of changes within the liver ranging from simple steatosis through to steatohepatitis and in extreme cases cirrhosis.[32] Steatohepatitis differs from simple steatosis in that significant inflammatory infiltrates are present in the liver commonly in association with ballooning degeneration of hepatocytes.[33]

The link between chemotherapy use and fatty liver disease was first reported in the literature in 1998. In a series of 21 patients with colorectal liver metastases treated with systemic 5-FU Peppercorn et al. reported that 48% (n=10) of patients had developed radiological evidence of steatosis on follow-up imaging.[34] In a later series Pawlik et al. reported the histological findings in the liver parenchyma of 334 patients who had undergone resection of colorectal liver metastases, 153 of whom had received pre-operative chemotherapy. In this study steatosis ≥ 30% (i.e. steatosis affecting more than 30% of hepatocytes) was present in 18.4% of patients who received pre-operative chemotherapy as compared to only 3.4% of patients who were chemotherapy naive (p=0.004). In particular the authors observed that steatosis was most strongly associated with Irinotecan based chemotherapy (27.3% of patients; p<0.001) than 5-FU monotherapy (14.9%; p=0.03) and lastly Oxaliplatin based chemotherapy

(9.6%; p=0.04) suggesting that the nature of the chemotherapy regimen may be important in determining liver toxicity.[35]

In contrast however a separate series of 406 patients who underwent resection of colorectal liver metastases failed to demonstrate any association between the administration of pre-operative chemotherapy and the subsequent development of steatosis ≥ 30%. In those receiving Irinotecan based chemotherapy (n=94) there was however a dramatic increase in the incidence of steatohepatitis as compared to those patients who were chemotherapy naive (20.2% vs. 4.4%; p=0.001), a finding which was in contrast to the smaller study described above.[35, 36]

To more accurately determine the nature of the association between chemotherapy use and the development of fatty change within the liver our group undertook a systematic review and meta-analysis of the published literature. In this analysis it was not possible to demonstrate any association with chemotherapy use overall (Relative Risk 1.25; 95% confidence interval 0.99 – 1.57; p=0.15) or Oxaliplatin based chemotherapy (Relative Risk 0.98; 95% confidence interval 0.59 – 1.63; p=0.95) and the development of steatosis ≥ 30%. In the case of Irinotecan based chemotherapy there was a strong trend to an increased risk of steatosis > 30% (Relative Risk 2.51; 95% Confidence Interval 0.79 – 7.90; p=0.12) which was not statistically significant as a consequence of the heterogeneity within the included studies. In contrast there was a strong association between Irinotecan based chemotherapy and steatohepatitis (Relative Risk 3.45; 95% Confidence Interval 1.12 – 10.62; p=0.03) which was not demonstrated with other regimens.[37]

2.2. Sinusoidal obstruction syndrome

Sinusoidal obstruction syndrome (SOS; previously known as hepatic veno-occlusive disease) represents a microvascular injury to the liver characterised by the histological findings of dilatation of the hepatic sinusoids and associated atrophy of the surrounding hepatocytes. In more advanced SOS these changes are accompanied by the development of regenerative nodules within the liver and ultimately peri-sinusoidal liver fibrosis.[38] Historically SOS was described as a condition occurring after ingestion of pyrrolizidine alkaloids, a group of compounds found in plants used in traditional African herbal remedies.[39, 40] Furthermore SOS has been reported to occur in up to 50% of patients receiving myeloablative chemotherapy prior to bone marrow transplantation.[41, 42]

In a seminal paper in 2004 Rubbia-Brandt published a report of histological changes in the liver parenchyma of 153 patients who had undergone resection of colorectal liver metastases. In this study it was reported that 44 out of 87 patients treated with pre-operative chemotherapy had histological features of SOS, the majority of whom had received treatment with Oxaliplatin based regimens.[38] Similar results were reported by Vauthey et al who demonstrated a significantly increased incidence of SOS in patients receiving Oxaliplatin based chemotherapy as compared to those who were chemotherapy naive (18.9% vs. 1.9%; p<0.001) where as no such association was demonstrated with other chemotherapy regimens.[36] In our systematic review of the published literature we demonstrated a strong association between Oxaliplatin based chemotherapy and SOS (Relative Risk 2.78; 95%

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Confidence Interval 1.35 – 5.69; p=0.0007) which again was not replicated in patients receiving alternative chemotherapy regimens.[37] The typical appearances of an Oxaliplatin injured liver, as encountered at laparotomy, are shown in Figure 1.



Figure 1. The classical appearance of the Oxaliplatin injured liver with SOS – commonly described as a "blue liver"

It is therefore clear from this discussion that the nature of liver injury following administration of chemotherapy to patients with colorectal liver metastases is dependent on the nature of the regimen administered. Irinotecan based regimens are primarily associated with the development of hepatic steatosis/steatohepatitis whereas Oxaliplatin based regimens are associated with the development of SOS. The assessment of the severity of this liver injury and its implications for the surgical management of these patients forms the discussion in the remainder of this chapter.

3. Assessment of the post-chemotherapy liver

Post hepatectomy liver failure (PHLF) is a feared complication of major liver resection and was recently defined as "a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions"[43] whose presence is associated with a dramatic increase in the risk of post-operative mortality.[44, 45]

A key risk factor for the development of PHLF is the presence of background liver disease or injury. Belghiti et al reported, in a series of 747 patients undergoing liver resection, that the presence of either cirrhosis or steatosis affecting more than 30% of hepatocytes (n=253) was associated with a post-operative mortality of 9.5% as compared to only 1% in those with a normal liver parenchyma.[46] In a series of 406 patients undergoing resection of colorectal

liver metastases Vauthey et al reported that those patients with steatohepatitis (n=34) experienced an increase in both 90 day mortality (14.7% vs. 1.6% p = 0.001) and post hepatectomy liver failure (5.8% vs. 0.8%; p=0.01).[36] The findings from these case series have been supported by a meta-analysis of the published literature which demonstrated that the presence of hepatic steatosis > 30% was associated with an increased risk of peri-operative complications (risk ratio 2.01; p<0.0001) and mortality (risk ratio 2.79; p=0.02).[47] Similarly the presence of SOS has been associated with an increased incidence of PHLF in a series of 51 patients undergoing resection of CRLM, 38 of whom had histologically proven SOS (68% vs. 23%; p=0.004)[48]

The other factor that is pivotal in determining the risk of PHLF is the volume of liver which will remain following surgery, commonly referred to as the future liver remnant or FLR, which can often be estimated pre-operatively by CT volumetry.[49] In 2003 Shoup et al reported a series of 126 patients who had undergone a liver resection to treat colorectal liver metastases. In those patients with a FLR of ≤ 25% (n=20) 90% developed PHLF as compared to 19% of those with an FLR > 25%. Logistic regression analysis demonstrated that the presence of an FLR<25% tripled the risk of PHLF (Odds Ratio 3.09; p<0.0001). Similarly in a study of 119 patients with a normal liver parenchyma undergoing major liver resection (i.e. resection of 3 or more Couinaud segments) the median FLR in the 7 patients who developed PHLF was 29.6% as compared to 42.5% in those who did not (p=0.009).[50] As a consequence of this evidence the minimum safe FLR in patients with an otherwise normal liver undergoing resection of CRLM is 25%.[51]

In those patients presenting for surgery on the background of multiple cycles of pre-operative chemotherapy it is pivotal, particularly when an extensive liver resection is planned, to minimise the risk of PHLF. When significant parenchymal injury is present it may be necessary for the FLR to be as high as 40% and this may have a significant impact on the surgical strategy employed.[52] Careful pre-operative assessment of the liver is therefore essential in these patients and the techniques which can be employed for doing this are discussed in more detail below.

3.1. Clinical/biochemical markers of chemotherapy induced liver injury

Identifying those patients at risk of steatohepatitis following Irinotecan based chemotherapy is particularly difficult not least because a significant proportion of patients in the background community will have a fatty liver as a consequence of either the metabolic syndrome, other underlying liver disease or lifestyle. This is reflected in the study of Ryan et al. which analysed histological changes in the liver of 334 patients undergoing resection of colorectal metastases. Only 8 patients in this study had histologically defined steatohepatitis the presence of which, on multivariate analysis, was found to be independently associated with a BMI > 30kg/m^2 but not the use of chemotherapy.[53] The study of Vauthey et al. reported that, in 94 patients treated with Irinotecan, the incidence of steatohepatitis was 12.1% in those with a BMI of < 25kg/m^2 but 24.6% in those with a BMI of ≥ 25kg/m^2. This study did not however undertake a multivariate analysis to identify independent risk factors associated with the presence of steatohepatitis.[36] It has been proposed that elevated serum transa-

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minases may be of use in determining simple steatosis from steatohepatitis in patients with non-alcoholic fatty liver disease but it is not know whether this observation also holds true in those with chemotherapy associated steatohepatitis.[54-56]

Whilst one might intuitively expect that there would be a direct correlation between the number of cycles of chemotherapy received and the presence of liver injury this relationship is in fact less than clear cut. In the study of Vauthey et al. which reported the presence of liver injury in 406 patients undergoing resection of colorectal metastases there was no association between the number of cycles of chemotherapy administered and the incidence of steatohepatitis or SOS.[36] On the other hand Kishi et al., in a series of 219 patients who were treated pre-operatively with Oxaliplatin based chemotherapy, reported that SOS was present more frequently in those who received 9 or more cycles of chemotherapy than those who did not (42% vs. 26%; p=0.017).[57] Similarly the study of Aloia et al. reported that the incidence of SOS in those receiving greater than 12 cycles of chemotherapy was 50% as compared to 25% in those receiving 6-12 cycles and 10% in those who received less than 6 cycles (p=0.01).[58] Several studies have undertaken multivariate analysis to identify independent risk factors associated with the development of chemotherapy induced liver injury. Nakano et al demonstrated that the presence of SOS was independently associated with receiving 6 or more cycles of Oxaliplatin based chemotherapy (Relative Risk 3.2; p=0.048).[59] In contrast however 3 other studies have failed to demonstrate any such independent association between the number of cycles of Oxaliplatin administered and the development of SOS.[48, 60, 61] This raises the question of whether other variables, such as the presence of underlying liver disease, also make a significant contribution to the development of chemotherapy induced liver injury.

Some authors have suggested that tumour related factors may play a role in determining the development of SOS. On a univariate analysis of 78 patients treated with pre-operative Oxaliplatin based chemotherapy Soubrane et al. reported that those with SOS tended to have a larger tumour size (7.8cm vs. 5.2cm; p = 0.004) although this was not identified as an independent risk factor on multivariate analysis.[48] Tamandl et al. were able to confirm this observation in a separate study and on this occasion they were able to demonstrate that a tumour size > 5cm was independently associated with the development of SOS on multivariate analysis (Hazard Ratio 4.42; p = 0.012).[61] This clinical data is supported by experimental data from our group which suggests that the presence of tumour within the liver of mice treated with Oxaliplatin based chemotherapy accelerates changes in gene expression associated with the development of SOS.[62]

The role of various haematological and biochemical parameters to predict the presence of SOS has also been explored in several studies. Soubrane et al. reported on univariate analysis that an elevated AST (p=0.0009), ALT (p=0.02) and a low platelet count (p<0.0001) were all suggestive of the presence of SOS. On multivariate analysis they demonstrated that a high AST to platelet count ratio (APRI score) was an independent predictor for the presence of SOS (Odds Ratio 5; p<0.005).[48] Similarly a multivariate analysis from Nakano et al. demonstrated an independent association between an elevated AST and the presence of SOS (Relative Risk 3.86; p=0.044). [59] Tamandl et al. reported that on multivariate analysis on

multivariate analysis an elevated alkaline phosphatase or γGT was an independent predictor of SOS (Hazard Ratio 4; p=0.038) although this was not true for AST or ALT.[61]

Whilst none of these studies have demonstrated a single factor that is reliably able to predict the presence of chemotherapy induced liver injury it is possible to begin to develop a picture of the patient characteristics which may lead to a raised index of suspicion and prompt a more thorough assessment of the liver parenchyma prior to surgery.

3.2. Radiological assessment of chemotherapy induced liver injury

The volume of data on the radiological assessment of fatty liver disease is vast and this is a reflection of the high incidence of non-alcoholic fatty liver disease in the general population. The consequence of this is that the appearances of fatty liver disease on each of the 3 main imaging modalities of the liver have been well described and is summarised in Table 1. It should be pointed out that on CT scanning hepatic steatosis is best detected on unenhanced images which are often not performed routinely in most imaging protocols in order to minimise patient radiation exposure.[63] A recent systematic review and meta-analysis of the published literature concluded that MRI represented the most accurate method for determining the extent of hepatic steatosis with a reported sensitivity of 97.4% and specificity of 76.1% for the detection of steatosis >30%.[64]

Imaging Modality	Characteristic features hepatic steatosis
Ultrasound	Intracellular fat accumulation leads to an increase in liver echogenicity [63]
Computed Tomography	Steatosis leads to a decrease in attenuation of the liver parenchyma [63, 65]
Magnetic Resonance Imaging	A loss of liver signal intensity occurs on T1 weighted gradient echo (GRE) opposed images[63, 65]

Table 1. Appearances of hepatic steatosis on the main liver imaging modalities

Several studies have attempted to identify the utility of pre-operative cross sectional imaging to identify hepatic steatosis specifically in patients undergoing liver resection. The first of these was published in 2008 by Cho et al. who conducted a retrospective analysis of 131 patients undergoing partial hepatectomy over a 4 year period who had one of either a non-contrast CT scan (n=26), contrast enhanced CT scan (n=74) or a gradient opposed MRI (n=32) with a median interval between imaging and surgery of 17 Days. The ability of these imaging modalities to predict histologically defined steatosis > 30% was determined. The authors demonstrated that of the two CT methods studied only non-contrast CT was of any utility in determining the presence of hepatic steatosis with a high degree of specificity (100%) but had low sensitivity (33%) with a corresponding positive predictive value (PPV) of 100% and negative predictive value (NPV) of 83%. In contrast MRI fared much better in excluding the presence of hepatic steatosis with an NPV of 94% but a PPV of only 44% with a sensitivity of 88% and specificity of 63%. The conclusion of this study was that cross-sectional imaging

alone was not consistently able to determine the presence of hepatic steatosis and was therefore of limited utility for this purpose.[66]

In 2009 O'Rourke et al. reported a prospective study of n=37 patients undergoing resection of colorectal liver metastases who received pre-operative liver specific MRI. Again this study demonstrated a much better performance for MRI in determining the presence of hepatic steatosis > 30% with a PPV of 100%, NPV of 87% a sensitivity of 63% and a specificity of 100%.[67] A subsequent retrospective study by Marsman et al compared the ability of non-contrast enhanced CT (n=32) and MRI (n=36) to detect the presence of histologically defined steatosis > 33% in patients undergoing resection of colorectal liver metastases after receiving pre-operative chemotherapy. In this study MRI by far out performed CT in terms of sensitivity (78% vs. 70%), specificity (100% vs. 86.4%); PPV (100% vs. 70%) and NPV (93.1% vs. 86.4%) suggesting that this is the imaging modality of choice.[68]

On the basis of the currently available evidence it appears that MRI is the imaging modality of choice to assess the extent of hepatic steatosis in patients with colorectal liver metastases prior to surgery. It must be highlighted that cross-sectional imaging is not able to differentiate between simple steatosis and steatohepatitis which can only be achieved with histological assessment of the liver. Furthermore a 'normal' imaging study does not exclude the presence of hepatic steatosis and in those cases where there is a high level of clinical suspicion a further evaluation of the liver must be undertaken.

The role of cross-sectional imaging in detecting the presence of SOS is much less clear cut as compared to hepatic steatosis. It has been proposed that the development of splenomegaly on post-chemotherapy imaging may serve as a surrogate marker for the presence of SOS. Overman et al conducted a study in patients who received either 5-FU/Oxaliplatin (n=96) or 5-FU alone (n=40) as adjuvant therapy following resection of a colonic primary and compared spleen size on pre-operative imaging to that 6 weeks after the final cycle of chemotherapy. They demonstrated that the median increase in spleen size was 22% for those patients receiving 5-FU/Oxaliplatin whereas there was no increase in size in those receiving 5-FU alone ($p<0.001$). The authors went on to look at a subgroup of patients (n=63) who underwent a liver resection after 5-FU/Oxaliplatin and demonstrated, on multivariate analysis, that a greater than 50% increase in spleen size following chemotherapy was independently able to predict the presence of SOS (Odds Ratio 2.34; $p=0.02$) with a sensitivity of 43%, and specificity of 90%.[60]

Several authors have explored the utility of various MRI protocols to predict the presence of SOS. Ward et al. reported a study of 60 patients with colorectal liver metastases who underwent superparamagnetic iron oxide (SPIO) enhanced MRI prior to liver resection. Following SPIO administration SOS is characterised by reticular hyperintensity on $T2^*$-gradient response echo weighted MRI images the presence of which the authors graded on a scale of 0 – 3 (summarised in Table 2) with a score of 2 or greater indicating the presence of SOS. Using this technique 24 of the 60 patients were thought to have SOS on the basis of MRI the presence of which was subsequently confirmed histologically in 20 patients. Of the 36 patients thought not to have SOS on the basis of MRI 3 were subsequently found to have histological features of SOS. This means that SPIO enhanced MRI, in this study, had a sensitivity

of 87%, specificity of 89%, PPV of 83% and NPV of 92% for the presence of SOS.[69] In contrast to these findings however O'Rourke et al. in their study of 37 patients found that SPIO enhanced MRI had a high specificity (100%) and PPV (100%) for the presence of severe SOS but a low sensitivity (11%) with a NPV of 78% suggesting that this technique may fail to identify a significant proportion of patients with SOS.[67]

Grade	Description
0	Absent
1	Fine reticulations on a minority of sections
2	Diffuse reticulations or localised coalescent areas of high signal
3	Diffuse reticulations present on all sections or densely coalescent areas of high signal on multiple sections

Table 2. Grading of reticular hyperintensity on SPIO enhanced MRI to determine the presence of SOS[69]

Shin et al. explored the ability of Gadoxetic acid disodium (EOB-MRI; Primavist®) enhanced MRI to detect the presence of SOS prior to resection of colorectal metastases. On EOB-MRI the presence of SOS appears as reticular hypointensity which the authors graded on a scale of 1-5 with a score of 4 (probably present) or 5 (definitely present) being considered diagnostic of SOS. Of the 42 patients included in this study all 12 MRI identified cases of SOS had the diagnosis confirmed histologically and of the 30 MRI negative cases 4 had histological evidence of SOS. This resulted in a sensitivity of 75%, specificity of 100%, PPV of 100% and a NPV of 87%. The images in this study were independently reviewed by a radiological resident with a good level of agreement (weighted kappa 0.765) suggesting that this technique is subject to minimal interobserver variability.[70]

The small number of patients in these studies make it difficult to recommend the routine use of any of these MRI protocols for the sole purpose of detecting pre-operative SOS. The presence of splenomegaly on pre-operative imaging, particularly in patients who have received multiple cycles of Oxaliplatin based chemotherapy, should raise suspicion about the presence of SOS and prompt a thorough assessment of the liver parenchyma if extended resection is to be performed.

3.3. Functional assessment of the future liver remnant

A variety of techniques have been described which aim to quantitatively assess the functional reserve of the liver and thereby provide a means to determine the minimum safe FLR that is required to avoid the risk of PHLF. Perhaps the most widely described of these techniques is the Indocyanine Green (ICG) retention test. Following injection ICG is transported in the systemic circulation bound to albumin and does not leave the serum until it reaches the liver where it is taken up by hepatocytes. These hepatocytes then clear ICG by excreting the compound into the biliary system in an ATP dependent manner. ICG does not enter the portal

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circulation nor is it metabolised by hepatocytes prior to its excretion and therefore the clearance of ICG provides a direct measure of hepatocyte function.[71]

Typically the retention of ICG at 15 minutes is measured in a serum sample (ICGR-15) and this value is used as a measure of hepatic functional reserve with a value of <10% being considered normal. Based on their experience of using this test in a series of 1429 patients Imamura et al. described the maximum extent of liver resection they thought could be safely performed according to the ICGR-15 value (see Table 3).[72] Others however view this ICGR-15 value as too conservative and state that a cut off of <14% should be used to identify those patients in whom it is safe to perform major liver resection.[73] The use of ICG retention as a pre-operative assessment of liver function is however predominantly limited to Asia where the majority of liver resections are performed for hepatocellular carcinoma and therefore the data regarding the validity of this test in patients with colorectal liver metastases is limited.

ICGR-15 Value	Typical Safe Liver Resection
<10%	Right/Left Trisectionectomy
10 – 19%	Left hepatectomy / Right sectorectomy
20 – 29%	Segmentectomy
≥ 30%	Limited non-anatomical resection

Table 3. Typical safe liver resection volumes as recommended by Imamura et al based on ICGR-15 values[72]

Nakano et al reported the outcome of 36 patients who underwent major hepatectomy (>3 Couinaud segments) 20 of whom had histologically proven SOS and 16 who had a normal liver parenchyma. The presence of SOS in these patients was independently associated with an ICGR-15 of >10%. It is of note that these patients experienced an increased risk of perioperative complications (40% vs. 6.3%; p=0.026) and a longer mean hospital stay (17 days vs. 11 days; p = 0.006).[59] Experimental studies have also suggested that ICGR-15 may be a useful measure of hepatocyte function in the context of hepatic steatosis.[74] In a series of 101 patients undergoing liver resection for colorectal metastases Klinger et al reported that the use of preoperative chemotherapy (n=83; all regimens) was associated with a longer ICGR-15 (7.3% vs. 3.5%; p = 0.005). Similarly those who had received pre-operative chemotherapy were more likely to have an ICGR-15 ≥ 10% (27.7% vs. 0%; p=0.011) and this was associated with an increased rate of post-operative complications (39.1% vs. 12.8%; p=0.005). No attempt was made in this study to correlate ICGR-15 values with histological changes within the liver parenchyma.[75]

The LiMAx test has recently been described as an alternative means of assessing the hepatic functional reserve. This test measures the cytochrome P450 mediated metabolism of ^{13}C labelled methacetin into acetaminophen and $^{13}CO_2$ which is exhaled. The test measures changes in the ratio of exhaled $^{13}CO_2$: $^{12}CO_2$ over a 60 minute period – the greater the $^{13}CO_2$ excretion the greater the functional reserve of the liver.[76] The authors have demonstrated

that low post-operative LiMAx values (<80μg/kg/h) are correlated with an unacceptable risk of post-operative morbidity. On the basis of this they have proposed an algorithm to determine the safety of liver surgery based upon pre-operative measurement of the LiMAx to calculate the likely post-operative LiMAx using CT volumetric calculations of the FLR. This strategy has not however been proven in an independent prospective cohort and therefore cannot currently be recommended for routine clinical use.[77]

A final technique for assessing the functional reserve of the liver is hepatobiliary scintigraphy using ^{99m}Tc-mebrofenin. Following injection ^{99m}Tc-mebrofenin is taken up by hepatocytes and excreted directly into the biliary system without prior intracellular metabolism in a similar manner to ICG. The hepatic uptake and excretion of ^{99m}Tc-mebrofenin is determined using images obtained with a gamma camera and from this it is possible to determine the total liver uptake, corrected for body surface area, as a %/min/m^2 of the total injected dose (referred to as the total liver function or TL-F). In addition the FLR uptake function (FLR-F) can be calculated as a function of the TL-F based on uptake in the calculated.[78]

De Graaf et al. reported a series 55 patients judged to be at high risk of post-operative complications following liver resection assessed with ^{99m}Tc-mebrofenin scintigraphy prior to liver resection. They demonstrated that TL-F was significantly reduced in those patients with background parenchymal disease (7.4 vs. 8.5 %/min/m^2; p=0.007). In addition the FLR-F was significantly lower in those patients who developed PHLF as compared to those who did not (2.2 vs. 4.3%/min/m^2; p=0.001).[79] Whilst this technology needs further evaluation in prospective studies it is likely that the emerging ability to perform single photon emission computed tomography (SPECT) thereby enabling quantification of tracer compound activity in combination with standard CT will lead to renewed interest in the technique.

At present none of these technologies have been adequately characterised in patients with colorectal metastases undergoing liver resection. Whilst they undoubtedly have potential merit in identifying those patients with an impaired hepatocyte mass it is not known whether the information they add is superior to that obtained standard clinical and radiological assessment. This must be established before the routine integration of these technologies into the assessment of this cohort of patients can be recommended.

4. Surgical management of the chemotherapy injured liver

When either clinical suspicion or pre-operative imaging suggest the presence of a chemotherapy induced injury to the liver it may no longer be possible to resect all metastatic disease whilst maintaining an adequate FLR to avoid the risk of liver failure. In this situation two key surgical strategies have been described to reduce the risk of surgery i.e. pre-operative portal vein embolisation and two-stage hepatectomy and these are discussed in more detail below.

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4.1. Pre-operative portal vein embolisation

Portal vein embolisation (PVE) is a particularly useful technique in patients who have disease which is technically resectable in a single operation but where so doing would lead to a compromised FLR. As early as 1920 Rous and Larimore observed that if they ligated a single branch of the portal vein in a rabbit there was atrophy of the ipsilateral lobe and hypertrophy of the contralateral lobe.[80] As a clinical technique PVE was initially described by Kinoshita et al. in 1986 as a means of limiting the extension of tumour thrombus in patients with hepatocellular carcinoma.[81] Subsequently in 1990 Makuuchi et al. demonstrated the safety and efficacy of this technique as a means of increasing the FLR in a series of 14 patients undergoing resection of hilar cholangiocarcinoma.[82] In a prospective study Farges et al. performed CT volumetry on patients undergoing pre-operative PVE and demonstrated that in those patients with no underlying parenchymal disease the typical increase in FLR was 16% whereas in those with chronic liver disease the typical increase in FLR was 9%.[83]

In 2010 Wicherts et al. reported a retrospective series of 67 patients who underwent liver resection for colorectal metastases after pre-operative PVE with a cohort of 297 patients who did not receive PVE. The authors observed that those patients treated with pre-operative PVE demonstrated a significantly higher complication rate (55.5% vs. 41.1%; $p = 0.035$) although there was no difference in surgical mortality between groups. Whilst this difference in morbidity is striking it is difficult to interpret since whilst all patients in the study underwent a major hepatectomy (≥3 Couinaud segments) 54% of those in the PVE group underwent a right trisectionectomy as compared to only 28% in the control group. What was striking in this study however was that 32 of the patients treated with PVE did not proceed to surgery and amongst these patients there were no 3 year survivors as compared to a 3 year survival rate of 44% in those who did undergo surgery.[84]

A similarly designed study by Pamecha et al. compared the outcome of 36 patients treated with pre-operative PVE with 65 patients who did not receive PVE all of whom had a diagnosis of colorectal metastases. Of the 36 patients treated with PVE 12 did not progress to surgery and had a median survival of 14 months as compared to 42 months in those who did progress to surgery ($p<0.0001$). Again there was a tendency to higher morbidity in the PVE group (36% vs. 20%) but in a similar manner to the study of Wicherts et al. more of these patients had undergone a right trisectionectomy (22% vs. 11%).[85]

The most important finding in both of these series is that nearly a third of all patients selected to undergo pre-operative portal vein embolisation do not undergo subsequent surgery and this is primarily a consequence of disease progression.[84, 85] It is likely that the most important factor driving this disease progression is the compensatory increase in arterial blood flow which occurs in the embolised lobe.[86] The blood supply of colorectal metastases is predominantly derived from the hepatic artery[87] and it is probable that the increase in arterial flow results in increased oxygen and nutrient supply to the tumour. In addition following PVE there is an increase in the hepatic production of a wide variety of cytokines, growth factors and other humoral factors that mediate liver regeneration and it may be that these also contribute to the progression of metastatic disease.[88, 89]

In summary PVE is a potentially useful technique for increasing the FLR in patients in whom this is likely to be compromised there is a significant risk that the procedure will result in disease progression rendering the patient inoperable and therefore must not be embarked upon lightly.

4.2. Two-stage hepatectomy

For a proportion of patients presenting with bilobar disease it is not possible to clear the entire tumour burden by an extended resection alone (e.g. right trisectionectomy) but rather it is necessary to combine an anatomical resection (e.g. or the right lobe) with multiple metastectomies from the contralateral lobe potentially resulting in an insufficient FLR, particularly in patients with a background liver injury (Figure 2). In such circumstances a PVE alone would not be appropriate because of the significant risk of tumour progression in the FLR and therefore a two stage resection should be considered. In the scenario described above this would typically consist of an initial operation to clear the left liver of tumour using multiple metastectomies followed several weeks later by a right hepatectomy. If it was felt at the time of the primary operation that the hypertrophy induced by surgery alone would not leave an adequate FLR for the second operation then it may be desirable to perform either intra-operative ligation of the right portal vein or post-operative percutaneous portal vein embolisation.[90] In this situation it is the authors preference to perform the latter procedure thereby avoiding unnecessary dissection of the hilum prior to right hepatectomy.

Wicherts et al. reported the outcomes of 59 patients considered to be inoperable using a single stage procedure who were selected for a two stage approach. All of these patients underwent a primary surgical procedure which in the majority of cases consisted of a minor hepatectomy (<3 Couinaud segments resected) the aim of which was to clear the left liver of tumour. Subsequently 42 patients underwent a second procedure which was typically a major hepatic resection (≥3 Couinaud segments) and typically this took place 3 months after the initial surgical procedure. It is of note that 17 patients selected for this approach did not undergo a second procedure primarily as a consequence of disease progression. The overall 5 year survival in this series was 31% when analysed on an intention to treat basis and this did not differ, in a statistically significantly manner, from patients undergoing a single stage hepatectomy over the same period in the authors unit.[91]

More recently Narita et al. reported the outcome of 79 patients treated using a two stage approach. After the initial surgical procedure 75 of these patients were considered appropriate to proceed to the second operation although the majority (92%) were thought to require portal vein embolisation to facilitate this. Of that cohort of patients 61 (78% of the original cohort) eventually underwent a successful second operation. The main reasons for patients not proceeding to a second procedure were tumour progression in 10 cases and insufficient regeneration of the FLR in a further 5 cases. It is of note that almost 1:6 of the patients who underwent a second surgical procedure were found to have new disease in the previously cleared FLR although this was dealt with at the time of surgery in all cases. In those patients who underwent a successful two stage resection the overall 5 year survival was 32%. Of the 61 patients who were treated successfully by a two stage approach 11 went on to have a sub-

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sequent resection of lung metastases although this had no effect on overall survival when compared to the 50 patients who did not.[92]

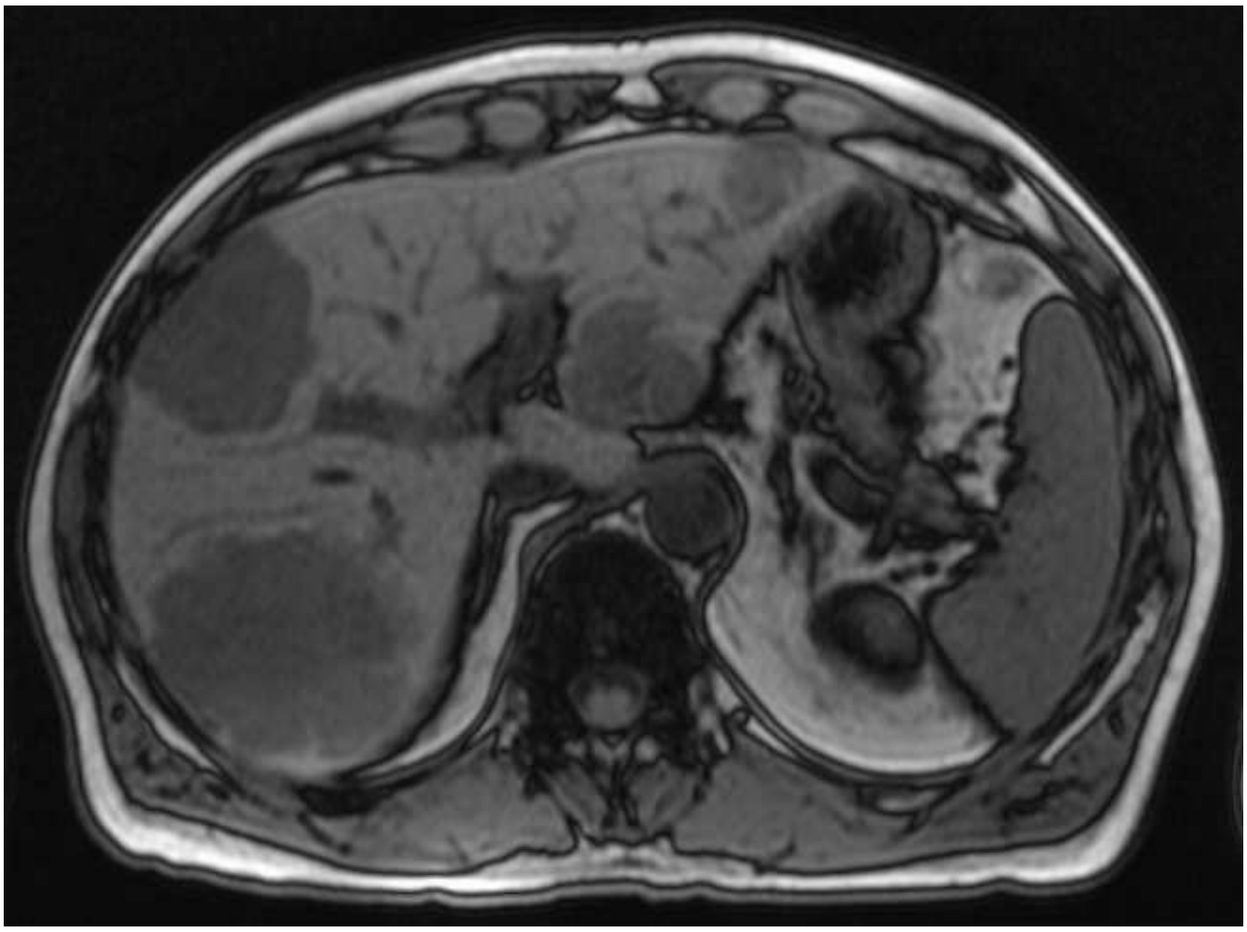


Figure 2. Typical MRI scan of patient with bilobar disease who would be considered suitable for a two staged approach to liver resection. With this distribution of disease a one stage approach would not leave an adequate FLR.

In a similar manner to PVE alone a two stage hepatectomy is a major undertaking and before embarking on this both surgeon and patient should be aware that there is a significant risk of not being able to complete the planned course of treatment. Despite this it does provide an opportunity to achieve a meaningful long term survival in selected patients with advanced disease.

5. The long term consequences of chemotherapy associated liver injury

Whilst the primary focus of this chapter is on the effects of chemotherapy associated liver injury on the surgical management of patients with colorectal liver metastases it would not be complete without some mention of the emerging evidence that this injury may have an effect on long term disease specific outcomes. Tamandl et al. have suggested that the pres-

ence of the histological features of SOS within the resected liver of patients with colorectal liver metastases may have a negative impact on long term disease specific survival. In particular patients with SOS demonstrated a significantly poorer 3 year progression free survival (6.7% vs. 22.7%; p=0.006) a finding which was upheld on multivariate analysis (Hazard Ratio 2.20; p=0.006). Specifically patients with SOS demonstrated a higher rate of intra-hepatic recurrence following surgery (66.7% vs. 30.5%; p=0.003) and not surprisingly this was associated with an increased risk of early all cause mortality on multivariate analysis (Hazard Ratio 2.90; p<0.001).[61]

A major criticism of the study of Tamandl et al. is that it includes only small numbers of patients (n=20 with SOS) and therefore it is difficult to draw definitive conclusions.[61] None the less a recent paper by Vreuls et al. has reported that the development of SOS may be associated with a poorer tumour response to Oxaliplatin based chemotherapy which the authors propose may be a consequence of tissue hypoperfusion leading to diminished leading to impaired delivery of chemotherapy to the tumour.[93] An alternative explanation may be that SOS is associated with increased expression of the chemokine CCL20 within the liver which is known to act as a chemo-attractant for colorectal cancer cells.[94] At the same time as this is occurring within the liver Oxaliplatin chemotherapy also results in increased expression of the CCL20 receptor CCR6 within colorectal liver metastases thereby increasing the migration and proliferation of tumour cells in response to CCL20.[95, 96] It may therefore be that the presence of SOS leads to the establishment of an autocrine signalling loop which favours the further growth and development of colorectal liver metastases.[97]

This emerging evidence is clearly a cause for concern and, if proven to be true, would add further impetus to the drive to develop strategies for the prevention of liver injury in patients being treated with systemic chemotherapy.

6. Conclusion

Advances in chemotherapy over the last decade or so have revolutionised the care for patients with colorectal liver metastases with the end result that patients who historically would have been considered inoperable are now able to undergo potentially curative surgical resection. The pay off for this advance has been the development of a chemotherapy associated injury to the liver the nature of which is determined the specific regimens used.

There is no specific test that is able to reliably detect the presence of an injured liver parenchyma and ultimately surgeons must maintain a high index of suspicion for its presence particularly in patients who have received multiple cycles of chemotherapy over a prolonged period of time. When a liver injury is present it is important that the surgical approach is considered carefully and makes allowances for the possibility of an impaired FLR with a subsequent risk of post operative liver failure. In those situations where there is a high risk of an insufficient FLR it may be appropriate to utilise techniques such as PVE or two stage hepatectomy although there is a risk with both these techniques of treatment failure as a consequence of disease progression.

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