Moser section: Advances in the surgical management of colorectal liver metastases

There have been considerable advances in the number of options available surgically for the management of colorectal liver metastases over the past two decades. As recently as the early 1990s, the management of a patient with colorectal liver metastases was largely palliative, and liver resection in these cases was considered controversial ([1]).

Evolving definition of resectability:

in addition to the acceptance that liver resection for colorectal metastases could offer our patients improved survival, the redefinition of resectability was also a significant advance. In the late 1990s, criteria were established for resectability that were based on the number and size of metastases, and the need to have a margin of 1 cm or even more (1). A more recent, unofficial definition is essentially to "remove all of the liver metastases and leave enough liver to survive". Specifically, a microscopically negative margin is sufficient, although recent evidence points to superior results with a margin of greater than 1 mm ([2]). There must be preservation of two contiguous functional liver segments with intact portal and arterial inflow, venous outflow, and biliary drainage. And finally, prior to embarking upon aggressive resections there must also be an adequate future liver remnant (FLR) ([3]). In cases where the FLR is felt to be insufficient, manoeuvres such as portal vein embolization or ligation can be employed to increase the FLR prior to resection.

Newer options for surgical resection of CRLM

There are many new options available for surgical or ablative clearance of the liver of liver metastases. In any given case, there are often more than one options possible, with each having its own advantages and disadvantages for discussion with the patient and at multidisciplinary tumor board rounds.

Ablation and two-stage procedures

Ablation techniques such as radiofrequency ablation and microwave ablation have been available since the 1990s and were helpful in a patient with one or two small metastases in the lobe contralateral to that being resected ([4]). This led to a modest increase in the resectability of colorectal liver metastases. Two-stage hepatectomy further improved resectability rates and was first reported in some large series in around 2000. This strategy included resection, followed by a period of one to six months to allow for regeneration to occur in the remaining liver before planning for the clearance of the remaining tumor on the second operation ([5]). However, regeneration was gradual, and in the time between operations, some patients experienced disease progression.

Portal vein embolization and ligation

Around the same time, portal vein embolization, done percutaneously, was introduced as a way of preparing for resection. The portal vein on the side planning to be resected was embolized with a variety of materials. Follow-up imaging could gauge the response in terms of atrophy of that lobe and

hypertrophy of the contralateral lobe. This was used in cases where the FLR was felt to be borderline or inadequate, as in some cases of tri-segmental resection ([6]).

The combination of two-stage hepatectomy along with portal vein embolization or ligation brought together the advantages of both approaches. Such a strategy made further significant gains in the resectability of colorectal liver metastases, reported in one institution as increasing from about 40% to about 70% of all patients being referred for colorectal liver metastases. ([7]).

Associating Liver Partition and Portal vein ligation for staged hepatectomy (ALPPS):

ALPPS is a strategy that was first attempted somewhat by accident when a planned two-stage procedure for a patient with bilobar colorectal liver metastases had to be aborted ([8]). The parenchyma had already been transected and the portal vein ligated, but the lobe that they had planned to resect was not yet removed. The patient was closed, and a CT scan done about one week after the abdomen was closed showed an incredible hypertrophy of the remaining left lateral segment, to almost double in size, along with significant atrophy of the right lobe. This was much more than would have been expected from simple portal vein ligation, and this accelerated regeneration over the span of one week is thought to be related to the transection and the raw surface that resulted.

The introduction of ALPPS further increased the apparent resectability of colorectal metastases to somewhere in the range of 80 or 85% (1). Unfortunately, the initial series of ALPPS procedures demonstrated a high rate of complications including rates of in-hospital mortality in some series in the 20 to 29% range. The rate of morbidity was reported around 50 to 80% ([9]). There were also high rates of early recurrence. More recent experience with ALPPS has fortunately shown reduced morbidity and mortality, as well as decreased recurrence rates.

Liver transplantation options:

Finally, in some large centres, and with very specific and strict criteria, liver transplantation is again being assessed as a possible treatment strategy for colorectal liver metastases ([10]). And other strategies taking advantage of regeneration of a small liver segment while the disease liver is still in situ, known as RAPID, have also been described (1).

Over the span of two decades, the resectability of colorectal metastases essentially went from 0%, to 20%, to 70%, and now up to 90% in patients without medical contraindications. This rapid increase in surgical options for the management of CRLM came out around the same time as the introduction of new chemotherapy regimens.

Chemotherapy for colorectal liver metastases: surgical implications

Nearly a full decade after the introduction of oxaliplatin-based chemotherapy for CRLM, a group of prominent CRLM surgeons and researchers penned an editorial, a cautionary note, detailing some of the effects of neoadjuvant chemotherapy that had been observed in patients undergoing liver resections ([11]).

Around that same time, a report on the histological findings in 174 CRLM liver resection specimens was published. They reported finding sinusoidal obstruction the liver surrounding the resected liver metastasis in 79% of patients treated with oxaliplatin. They also documented Nodular Regenerative Hyperplasia in 16% and steatosis in 49% ([12]).

Sinusoidal obstruction syndrome (SOS)

SOS is a condition previously observed in the form of venoocclusive disease (VOD) noted in patients undergoing chemotherapy prior to stem cell transplant. Microscopically, there is obvious injury to the endothelial lining of the sinusoids, thrombosis, and extravasation of red blood cells. Grossly, the congestion that results from obstruction of flow proceeding to the central vein gives the liver a mottled and bluish appearance.

Vauthey confirmed the association of oxaliplatin with SOS ([13]) and despite the dramatic bluish appearance of the liver in these cases, his group found no increase in ninety-day morbidity or mortality in 79 patients treated with oxaliplatin who had undergone resection.

Nakano et al reported in 2008 that about 52% of patients treated with oxaliplatin in their series developed SOS ([14]). They did note some increased morbidity in terms of grade 3 and grade 4 Clavien-Dindo complications (6.3% versus 40%, p=0.026), and an increased hospital stay, although both the sinusoidal injury positive and sinusoidal injury negative group were admittedly small, with fewer than 20 patients in each group.

The EORTC 40983 trial ([15]) was a multicentre randomized controlled trial comparing surgery only to (oxaliplatin-based) chemotherapy before and after surgery for upfront resectable CRLM. As in Vauthey's study, they noted a low rate of complications in the group receiving oxaliplatin-based chemotherapy prior to resection.

Soubrane in 2009 published the results of the retrospective look at patients who had undergone major hepatectomy following preoperative chemotherapy ([16]). Among those treated with oxaliplatin, 59% of these patients developed SOS. There was a trend towards increased blood loss and an increased volume of transfusion in the group with higher grade SOS, compared to the group with lower grade SOS. They did, however, see an increase in transient hepatic dysfunction (3/13 versus 26/38, p=0.004) and ascites as well. The only cases of severe liver failure were seen in patients with the high-grade SOS lesions.

Overall, in the two largest series, it would not appear that SOS is of great consequence to liver resection, although one must remember that most of the studies involved quite small groups, were retrospective, and were of course done in high-volume centres which may have a lower rate of complications in general.

Nodular regenerative hyperplasia (NRH)

NRH has some similarities and common associations with SOS. Grossly, a liver affected by NRH can look almost cirrhotic, and yet microscopically, it is notable for its nodularity in the absence of significant fibrosis. NRH is associated with sinusoidal dilatation and is also associated with oxaliplatin treatment.

Vigano ([17]) in 2015 reported on 406 patients with colorectal liver metastases undergoing resection after chemotherapy and identified 87 (18%) patients with NRH. NRH was found to be associated with an increased risk of (transient) liver failure (9% versus 2%, P equals 0.002), with higher risk associated with more major resection.

Steatohepatitis and steatosis

Steatohepatitis was documented in 20.2% of patients receiving irinotecan in a study of 248 patients receiving preoperative chemotherapy followed by liver surgery for CRLM (13). The same group also noted an increased risk of steatohepatitis in patients with a higher BMI. Patients in this series with steatohepatitis had a higher 90-day mortality post resection compared to those without steatohepatitis (14.7% versus 1.6%, OR equal 10.5, P equals 0.001). A case-control study of 102 patients with steatohepatitis matched to controls without steatohepatitis but having a similar extent of resection noted similar results ([18]). Those with steatohepatitis had an increased overall morbidity and a higher risk of hepatic decompensation.

Whether steatosis without the inflammatory cell infiltrate of steatohepatitis leads to an increased risk of morbidity or mortality has been controversial. However, a well constructed meta-analysis ([19]) suggests that the risk of complications is approximately doubled in patients with significant steatosis, whereas there is no obvious increase in mortality following liver resection compared to those patients without steatosis.

Bevacizumab:

Bevacizumab is often added to existing chemotherapy regimens for CRLM. The wound healing problems and wound infection risk in surgical patients is well known ([20]). Waiting for 5 to 8 weeks after the last dose of bevacizumab is advised and has reduced the incidence of these wound issues. As an added benefit, bevacizumab seems to have a protective effect against SOS. This was documented in a histopathological study of patients treated with oxaliplatin, with and without bevacizumab ([21]). The group documented a significant reduction in the incidence of grades 2 or 3 SOS when bevacizumab was added (62% versus 31%, P less than 0.001).

Limitations in the data surrounding CRLM

There are several limitations to the data surrounding surgical complications related to preoperative chemotherapy. Firstly, just like for any surgical research, there will always be a significant amount of surgical variation between centres and between surgeons at those centres. There is no consensus as to what constitutes resectable and unresectable, and any given case can have different approaches in terms of the transection device, the philosophy of major liver resection versus multiple wedge resections, and the extent to which a given institution uses PVE or PVL ([22]). Almost all the studies were retrospective and observational, and some drew conclusions based on relatively small numbers of patients.

Finally, one must recall that these reports generally came from high-volume centres. Although no increase in morbidity or mortality is reported for several of the post chemotherapy pathologies, it's quite possible that these differences may be more apparent in a small volume centre.

Should hepatic injury change surgical planning?

Steatohepatitis, in particular, seems to increase the morbidity and mortality of liver resection, whereas it's less clear that sinusoidal obstruction, in spite of the dramatic mottled blue liver appearance has any effect on surgical morbidity and mortality. And yet preoperative imaging and even needle biopsy are not particularly helpful. While imaging might identify steatosis in up to 50% of patients, it cannot distinguish the more serious steatohepatitis from steatosis. Likewise, the irregular distribution of the disease process in SOS makes it such that a needle biopsy can underrepresented the extent of disease elsewhere in the liver. The intraoperative appearance can help to make the diagnosis but doesn't give a full picture. While the intraoperative finding of steatosis would not likely cause most surgeons to abandon the procedure, these appearances might make one think very carefully about reducing the extent of liver tissue that's removed. Specifically, one might consider multiple wedge resections and ablation as opposed to a formal lobectomy in a very steatotic liver.

What is the ideal number of cycles of chemotherapy before resection?

Because of the changing and continually evolving chemotherapy agents and regimens, the data surrounding an ideal number of treatments prior to surgery has been quite heterogeneous. For cases where the goal is conversion therapy (the conversion of an unresectable situation into a resectable one), the number of chemotherapy treatments will be dictated by the response and either conversion to a resectable situation or disease progression. In those cases where neoadjuvant chemotherapy is contemplated in cases of resectable disease, a few studies have consistently suggested six or fewer cycles might be optimum, with morbidity increasing when more than six cycles are utilized ([23], [24]).

How long after chemotherapy should liver resection take place?

How long to wait after the final dose of chemotherapy before proceeding to liver resection likewise does not have a lot of evidence in the literature. This is a balance between more toxicity in the liver if operation takes place too soon after the last dose of chemotherapy, versus the risk of disease progression if the interval between chemotherapy and surgery is too long. The data is also quite heterogeneous. And yet several studies, generally retrospective, some with small groups, consistently suggest a time between five and eight weeks ([25]).

Reduction of the extent of an aggressive surgical resection and assessment of biological behavior

Although the oncologic data suggests improved disease-free survival but no obvious overall survival advantage to preoperative and postoperative chemotherapy for CRLM, there are some surgical reasons to consider neoadjuvant chemotherapy. With aggressive strategies including two-stage procedures with

or without portal vein embolization/ligation, or ALPPS, the majority of patients with CRLM can be considered resectable, however this will be at the cost of a really large operation and its attendant risks. In these cases, neoadjuvant chemotherapy might make it possible to reduce the extent/severity of the surgery, while at the same time acting as a biological test of time. The goal would be to assess the biological behaviour of the tumor. Conversely, a tumor that is seen as having better biological behaviour during the test of time of chemotherapy, on some level helps to justify a major resection. This test of time may be one of the reasons attributed to the improvement of ALPPS results over the last five years ([26]).

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