Colorectal Liver Metastases; The Current Scenario

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Received: 11 October 2010 / Accepted: 25 November 2010 / Published online: 19 April 2011
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Abstract Colorectal cancer is the most common gastrointestinal malignancy. When metastases occurs, it most frequently occurs in the liver. Median survival without any treatment is poor, and until recently only a subset of patients were amenable to any form of surgical therapy. The following article aims to examine recent strategies used to increase the cohort of patients coming to curative oncological surgery.

Keywords Colorectal metastases · Colorectal neoplasm · Metastases · Ablation

Colorectal cancer is the commonest gastrointestinal malignancy and the second commonest cause of cancer related death in western society [1]. The liver is most commonly the first site of metastatic disease; in fact as many as 20%–25% of patients will have clinically detectable liver metastases at the initial diagnosis of colorectal cancer [2]. A further 30%–40% will subsequently develop liver metastases, usually within 3 years of successful resection of the primary colorectal cancer [3].

The median survival without any form of treatment is only 6–8 months [3]. The prognosis is best for those with a limited number of metastases confined to a single lobe. However, even for the best prognostic group 5 year survival was limited. Surgical resection offers the only potential for cure and until very recently only 10%–20% of patients with metastases were considered suitable for resection.

The following review aims to outline a variety of recent strategies which have been used to increase the pool of

patients offered curative resections. In particular, the review will focus on pre-operative staging techniques, standards for surgical resection, novel surgical strategies, neoadjuvant chemotherapy and ablative techniques.

Pre-operative Staging

Computed Tomography (CT)

Recent advances in CT technology, such as helical CT and multidetector row helical CT have improved the performance of CT in terms of resolution and ability to image the liver during various phases of contrast enhancement with greater precision. Intravenous iodinated media should routinely be used as it helps characterise liver lesions based on their enhancement patterns during the various phases of contrast circulation in the liver [4].

CT has become the imaging modality of choice for evaluating suspected liver metastases. However, limitations include the need for radiation dose and low sensitivity for detection and characterisation of lesions smaller than 1 cm

Magnetic Resonance Imaging (MRI)

MRI is also a particularly effective imaging tool for characterising liver lesions. It typically provides high lesion-to-liver contrast without using ionising radiation. Typically, colorectal liver metastases show low signal intensity on T1-weighted images and moderately high signal intensity on T2-weighted images. Gadolinium (most commonly used MRI agent), behaves in a similar manner to iodinated contrasts used in CT scanning. Liver specific contrast media such as superparamagnetic iron oxide (SPIO) may further improve the contrast between normal

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liver parenchyma and metastases, as it is taken up by the Kupffer cells of the reticulo-endothelial system.

Limitations of MRI are that it has a low sensitivity for detecting extra-hepatic disease in the peritoneum and chest, in particular. However, it is very useful for differentiating indeterminate lesions detected on CT (fat infiltration vs small metastases vs small cyst). Additionally, it can be safely used in patients with allergies to iodinated contrasts [4].

Positron Emission Tomography (PET)

PET has emerged recently as an important diagnostic tool in the evaluation of colorectal liver metastases. A greater metabolic activity in malignant tissue is accompanied with a greater glucose uptake relative to that of the surrounding normal tissue. PET is highly sensitive; however any focal area of hypermetabolism can give rise to a false-positive. Other disadvantages include high cost, poor lesion localisation and limited sensitivity for lesions smaller than 1 cm. It is particularly useful in patients with a high likelihood of disseminated disease at presentation or in those with hepatic recurrence [5].

A recent pilot study by the authors found that the addition of PET-CT had not reduced the number of futile laparotomies performed. However, patients with extra-hepatic disease had been identified early and had had the extra-hepatic disease dealt with appropriately.

Staging Laparoscopy

The utility of staging laparoscopy has evolved over the course of time owing to the improvements seen in radiological techniques and changing indications for surgery. Additionally, it is highly sensitive for the detection of peritoneal metastases and liver surface metastases but less so for detecting locally advanced disease or nodal spread.

Surgery: Criteria for Resection

If curative resection can be achieved, then 5 year survival can approach up to 40%. In days gone by the decision to operate was fairly straightforward; liver resection was attempted only in patients who had between 1 and 3 unilobar metastases, presenting 12 months post resection of the primary, with at least a 1 cm margin of healthy liver parenchyma remaining, with no nodal or extra-hepatic disease.

However, recently experience has demonstrated that even patients with the perceived adverse factors can in fact have good survival outcomes post surgical intervention [6, 7]. Hence, a shift has occurred in the criteria used to assess resectability.

The American Hepato-Pancreatico-Biliary Association (AHPBA) 2006 consensus conference concluded that metastases should be deemed resectable if a) the disease can be completely removed, b) two adjacent liver segments can be spared with adequate inflow, outflow and biliary drainage and c) the volume of liver remaining after resection (Future liver remnant- FLR) is adequate. The FLR limit for safe resection in a patient with normal liver function is normally around 20% volume.

Additional criteria for unresectability are invasion of one branch of liver pedicle, and contact with the contra lateral branch, contact with the inferior vena cava, invasion of all three hepatic veins, the presence of coeliac lymph nodes and the presence of non-resectable extra-hepatic disease [8].

New Strategies to Improve Resectability

Portal Vein Embolisation

Portal vein embolisation (PVE) induces atrophy of the liver to be resected whilst inducing hypertrophy of the FLR. The primary purpose of this is to prevent post-resection hepatic insufficiency, liver failure and death. A recent meta-analysis of 1,088 patients confirmed that PVE significantly increases FLR. The overall morbidity was 2.2% with no mortality. Post PVE, 930 (85%) of patients underwent attempted hepatectomy. 158 (17%) did not undergo resection secondary to either disease progression or insufficient hypertrophy of the FLR [9].

Furthermore, PVE appears to be feasible even when combined with neoadjuvant chemotherapy [10].

Two Stage Hepatectomy

Similarly, two stage hepatectomy involves delayed re-hepatectomy after hypertrophy of the residual liver and may be used for large bilateral lesions, where a single stage hepatectomy would lead to liver failure [11].

The first stage involves the lesser resection of metastases from the FLR, followed by a period of liver regeneration and then typically PVE or chemotherapy. The second stage is performed 2–3 months later and involves a major hepatectomy

Repeat Hepatectomy

Repeat hepatectomy for patients with colorectal cancer is safe and provides survival benefit similar to that of a first time resection. A meta-analysis of 21 studies, comprising 3,741 patients showed that there was no difference in perioperative morbidity, mortality or long-term survival between patients undergoing a first or repeat hepatectomy [12].

Extreme Liver Surgery

Resection of tumours involving the hepatic vascular inflow have been described, utilising a variety of techniques including portal vein resection and reconstruction, hepatic artery resection and reconstruction (or arterialisation of the portal vein as an alternative) [13].

Resection of tumours with involvement of the inferior vena cava of the three major hepatic veins have also been performed, using techniques such as total hepatic vascular exclusion, in situ hypothermic perfusion and ex vivo (bench) hepatic resection [14, 15].

These techniques are not routinely practised in most centres. However, the fact that they are being performed offers hope to those with disease involving the IVC and hepatic veins.

Extrahepatic Colorectal Disease

Extrahepatic colorectal metastases may be resected with curative intent. Tumours such as adrenal metastases, pulmonary metastases and liver lesions with direct diaphragmatic invasion that are few in number can be readily resected. Reported long term survival following pneumonectomy for colorectal pulmonary metastases mirrors that seen post hepatectomy [16].

“Downstaging” of Colorectal Liver Metastases

In the past, 5-fluorouracil (5-FU) with folinic acid (leucovorin) was the only chemotherapy available for patients with unresectable colorectal liver metastases. However, this rarely provided sufficient intrahepatic tumoricidal effect to enable the tumour to be resected. Modern chemotherapeutic regimens combining 5-FU, folinic acid and oxaliplatin and/or irinotecan are associated with much higher response rates and can allow 10%–30% of patients with initially unresectable disease to become resectable [17–22].

The largest study reported thus [17], was a consecutive series of 1,104 patients who were initially considered unresectable and were treated with chemotherapy and had a good response to chemotherapy enabling 93% to subsequently undergo potentially curative hepatic surgery. Recurrence was frequent but treated in 52 patients by repeat hepatectomy (71 procedures) and by extra-hepatic resection in 42 patients (77 procedures). Survival was 33% and 23% at 5 and 10 years respectively.

Chemotherapy-Associated Steatohepatitis

The increasing use of neoadjuvant treatment has meant that chemotherapy-associated steatohepatitis (CASH) has become more commonplace. The term “blue liver syndrome” has

also been coined to describe the vascular alterations that result in a blueish discolouration, oedema and a sponge like consistency similar to that seen in early cirrhosis.

Objective evidence is derived from a recent study that compared 45 patients who received systemic chemotherapy less than 2 months prior to resection with 22 patients who did not receive any chemotherapy in the 6 months prior to resection [23]. There were no post operative deaths in either group, however, post operative complications were much higher in the chemotherapy group (17 out of 45 patients vs 3 out of 22). Liver failure occurred in five cases in the chemotherapy group but did not occur in the non-chemotherapy group. Furthermore, post operative morbidity was correlated with the number of cycles of chemotherapy administered prior to surgery. Pathological examination of the non-tumorous liver parenchyma was associated with vascular changes, such as sinusoidal dilatation, atrophy of hepatocytes and hepatocyte necrosis.

Other studies have shown that post operative complications are higher post chemotherapy. In a study that included 248 patients who received pre-operative chemotherapy, oxaliplatin was associated with sinusoidal dilatation and irinotecan was associated with steatohepatitis. Furthermore, patients with steatohepatitis had increased 90 day mortality [24]. Sinusoidal injury has been significantly associated with higher morbidity and longer hospital stays in patients with hepatic colorectal metastases who underwent major hepatectomies post oxaliplatin based therapies [25].

Clearly the introduction of neoadjuvant therapy will present many challenges, as well as significant benefits. It is clearly prudent to have a larger FLR (around 30%) post resection, in patients who undergo preoperative chemotherapy.

Adjuvant and “Perioperative” Chemotherapy

Adjuvant chemotherapy improves the cure rate in early stage colorectal cancer, indicating that it eradicates residual microscopic disease in some patients. As these are the source of ultimately fatal recurrences in patients who relapse post hepatic surgery, the logic of extrapolating adjuvant chemotherapy after early stage colorectal cancer to the resected metastases setting, appears sound. In a study evaluating chemotherapy with 5-FU, folinic acid and oxaliplatin (FOLFOX) 3 months before and 3 months after surgery, patients with initially resectable disease had improved outcome and progression free survival when compared with patients who were treated with surgery alone [26].

Hepatic Arterial Infusion

Hepatic arterial infusion chemotherapy (HAC) maximises hepatic drug exposure by delivering drugs via the hepatic

artery and by using agents with high first-pass hepatic extraction rates. The principle is based on the principle that metastases derive their blood supply largely from the hepatic artery, whereas the normal liver is supplied mainly by the portal vein. Trials of a multi-modality approach combining systemic chemotherapy with HAC have shown high response rates and raise the possibility of converting metastases that are unresectable and have progressed on prior systemic regimens to being resectable [27]. Obviously, further work is needed in this area.

Ablative Therapies

Although the cohort of patients who are amenable to surgical resection is increasing, unfortunately there remains a significant group of patients for whom surgery is not an option. This may be due to either patient co morbidities, anatomical location of the metastases or parenchymal properties. Hence, much attention has recently focussed on ablative technologies. Ablative therapies take many forms; cryotherapy, laser hyperthermia and ethanol injection have decreased in popularity due to either high complication rates or lack of efficacy. Radiofrequency and microwave ablation are now being increasingly deployed.

Cryotherapy

This involves the circulation of liquid nitrogen through metallic probes inserted into the tumour. This causes the rapid freezing of tissue to produce tumour necrosis. However, cryotherapy, as stated already, is declining in popularity due to its high complication rate and mortality rates of approximately 7%. Specific complications include major haemorrhage from cracking of the liver parenchyma/capsule and a syndrome of severe coagulopathy, disseminated intravascular coagulopathy and multi-organ failure [28].

Radiofrequency Ablation (RFA)

RFA has largely superseded cryotherapy due to its higher safety profile. However, its major limiting factor is the increased risk of recurrence locally in lesions greater than 2 cm.

RFA produces localised tumour destruction by means of an alternating current passing through the RFA needle to create local temperatures of 70–100°C, resulting in cell death through protein denaturation and microvascular injury [29].

Much of the recent interest in RFA is derived from its high safety profile. A meta-analysis of 95 published series reported a complication rate of 8.9%, with intra-abdominal bleeding, sepsis, and biliary tree injury being the commonest.

The mortality rates varied from 0% to 0.5% [29]. RFA has a high rate of local recurrence, ranging from 1.8% to 12% with a surgical approach and upto 40% via the percutaneous route. This is undoubtedly related to the type of lesions treated with RFA, which are often close to major vascular structures and hence are not suitable for resection with a clear margin. The vessels absorb some of the heat produced by the electrode, via a phenomenon known as the “heat sink” effect and hence the tumour is often incompletely ablated.

The efficacy of RFA in unresectable colorectal liver metastases has been established by several large cohort studies with median survivals of 29–36 months being reported [30].

Finally at the time of writing, Ruers and colleagues presented the final results of the EORTC CLOCC (EORTC 40004) Study at the 2010 ASCO meeting in Chicago. This study was conceived as a 400 patient Phase III randomisation of patients with up to nine unresectable liver-only metastases to receive oxaliplatin-based chemotherapy or chemotherapy plus RFA (open, laparoscopic or percutaneous) with or without concomitant resection of easily resectable lesions. The primary end-point was powered to test for a 38% overall survival benefit in the RFA arm. This was an extremely ambitious project, and recruitment was understandably extremely difficult. After a period of extreme frustration, the trial objective was reduced to a 100 patient randomised Phase II, with an actual accrual of 119 patients. However, it remains a unique landmark study, probably never to be repeated, and the only prospective study to address the question of the real survival benefit of thermal ablation therapy for metastatic liver disease.

Although there was a significant improvement in 3 year progression free-survival (PFS) of 27.6% for RFA +chemotherapy compared to 10.7% for chemotherapy alone ($p=0.025$), a secondary end point, overall survival (OS) at 30 months (the primary study end point) was no different for RFA+chemotherapy (63.8%) over chemotherapy alone (58.6%)($p=0.218$). It must be remembered that when designed, the study was never powered to demonstrate a significant result for its primary end point with such low numbers, and it is extremely unlikely that any investigators will ever be bold enough to try to repeat such a study. Therefore in the pragmatic real world, we must accept the evidence that we have which in our opinion suggests a survival benefit for thermal ablation therapies in the treatment of relatively low volume unresectable liver metastases.

Microwave Ablation

This has been designed to overcome the limitations of previous ablative techniques. Under imaging guidance, the

tumour is localised and a thin microwave antenna is placed directly into it. Tissue heating is based on the agitation of water molecules, which in turn cause cellular death via coagulation necrosis. Thus it is different to RFA as the frequency of the electromagnetic radiation used is considerably higher. This results in a greater ability to localise the dissipation of energy, though the tissue penetration is reduced. Microwave ablation offers many of the benefits of radiofrequency ablation, with some theoretical substantial advantages. These benefits include: a) higher intra-tumoral temperatures, b) faster ablation times, and c) ability to ablate larger tumour volumes [30, 31].

Author Experience

Our hepato-biliary unit is a tertiary referral unit covering the whole of Merseyside (UK) and parts of North Wales. To date, we have performed over 1,600 hepatic resections over the course of the past 7 years (the senior author, GJP, has performed over 900 hepatic resections). We have a 5 year survival of 43%, allied to a 10 year survival of 26%.

The primary point of referral is usually via colorectal surgeons. All patients referred to our unit are discussed at a weekly, specialist liver cancer multi-disciplinary meeting. This meeting is attended by hepato-biliary surgeons, anaesthetists, oncologists, radiologists, hepatologists and advanced hepato-biliary nurse practitioners. A consensus decision is made as to the optimal mode of further management. At this juncture, first line imaging (CT) would already have been performed and need for further imaging is decided.

The vast majority of cases performed within our unit have been straightforward hepatectomies. However, in order to improve rates of resectability we do deploy many of the techniques described. We undertake portal vein embolisation, perform two stage hepatectomies, undertake repeat hepatectomies and have performed several resections involving resection and reconstruction of the inferior vena cava. Additionally, in patients who were unfit for major surgery we have performed percutaneous radiofrequency ablation. However, if ablation is performed during open surgery (normally to extend the boundaries of resectability), we use microwave ablation due to the theoretical advantages it offers.

Conclusions

The key recent advancements in the management of hepatic colorectal metastases have been the availability of more effective chemotherapy regimens capable of rendering inoperable disease to be resectable. Concurrently, there has been a shift from doing “major resections” (ie three or

more segments) to performing parenchyma sparing metastectomies. Additionally, even patients with inoperable disease are able to undergo either ablation or palliative chemotherapy to extend their life expectancy.

However, there still remains significant room for further developments in the next few years.

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