REVIEW ARTICLE

Investigation and Management of Colorectal Cancer Liver Metastases

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Abstract

Colorectal cancer remains the third most common cancer worldwide and ranks 2nd in cancer-related mortality in developed countries. The liver is the first organ involved with metastatic disease after lymph node spread is excluded. Colorectal liver metastases (CRLM) are present in over 70% of patients dying from disseminated colorectal cancer. The approach to investigation and management of CRLM remains a complex area, in which practice is continuing to evolve with new evidence, and which ongoing research is ongoing. This review aims to provide a broad, up-to-date overview of the current landscape of the literature in regards to imaging modalities used in diagnosis and staging of CRLM, the multiple surgical management options available, as well as the adjunct therapies and chemotherapy regimens utilised.

1. Introduction

Colorectal cancer remains the third most common cancer worldwide, and ranks 2nd in cancer-related mortality in developed countries (1, 2). The liver is the first organ involved with metastatic disease after lymph node spread is excluded (3) and colorectal liver metastases (CRLM) are present in over 70% of patients dying from disseminated colorectal cancer (4). It is clear from several studies that the presence of CRLM is one of the most significant determinants of patient survival (5-7). Only 20-30% of patients with metastatic colorectal cancer will have isolated liver metastases that is suitable for resection, which remains the sole curative modality in CRLM (8). Even with surgical resection, recurrence rates have been reported as high as 70% (9, 10). However, five-year survival rates up to 50-60% have been reported following resection (11). Without surgery, median survival ranges between 6-8 months without chemotherapy and up to 30 months on chemotherapy (11). This review aims to provide an outline on current practices in the investigation and management of CRLM.

2. Diagnosis and Staging

CRLM are often diagnosed during investigations for staging or surgery for the primary colorectal cancer, or as part of a surveil-

lance protocol. Multiple imaging modalities exist with differing sensitivities and strengths. They are used in combination to diagnose CRLM, assess background liver disease, exclude extra-hepatic disease, and ultimately to evaluate feasibility for curative treatment or ablative therapy (10).

2.1. Ultrasound

Ultrasound is an inexpensive modality that is readily available, repeatable and avoids the exposure to radiation. It is a particularly useful and cost-effective modality in the detection of lesions suspected of being simple cysts or haemangiomas.

The reported sensitivities of ultrasound alone in detecting CRLM has been reported to be between 67.4%-74.6% (12). The advent of Contrast Enhanced Ultrasound (CEUS) greatly increased the viability of this modality in the assessment of CRLM, with sensitivity up to 95.8%, falling to 76.6% in lesions <1cm (12, 13). CEUS has been shown to detect up to 97% of lesions detected by Computed Tomography (CT) (14). However, CEUS remains a specialized examination which requires particular operator expertise, restricting its availability to a limited number of specialized centres. Furthermore, it often provides equivocal results in the presence of hepatosteatosis, for example in the post chemotherapy setting (13).

Intra-operative ultrasound (IOUS) may be performed at the time of resection of the primary cancer, prior to hepatic resection, to allow for assessment of liver parenchyma and to provide a more detailed appraisal of the relation of the tumour to adjacent biliary and vascular structures. A study by Scaife *et al.* reported that IOUS identified more tumours in 27% of cases compared with CT alone (15). The sensitivity of IOUS has been reported as high as 95.2% (16). In a recent series, its use resulted in an alteration in the surgical management of 29% of CRLM patients (17).

2.2. CT

CT remains a mainstay of pre-operative imaging in CLRM patients, with most presenting with at least a staging CT of the chest abdomen and pelvis with intravenous contrast. CRLM are typically hypovascular and appear hypodense compared with the surrounding hepatic parenchyma during the portal venous phase (18). However, 11% of liver metastases can appear calcified on initial CT imaging (19). Larger metastases may have faint rim enhancement during the hepatic arterial phase, differentiating them from haemangiomas (13). The sensitivity of contrast enhanced CT for the detection of CRLM is reported to be up to 71%, with specificity of 91% in one study comparing CT assessment by 3 radiologists of 237 liver lesions to histopathology post resection (20). A systematic review of 61 studies by Bipat *et al.* found the sensitivity of helical CT to be 64% (21).

Optimal CT slice thickness in detecting small CRLM has been suggested to be 2-4mm, with 1mm slices found to decrease image quality due to artifacts with no improvement in detection rates (13, 22).

The advantages of CT include its availability and reproducibility. In the context of advanced malignancy, consideration of radiation exposure is of less clinical relevance, although renal impairment and contrast allergies still need to be considered (13). CT is also useful in determining other sites of metastases. However, it should be noted that CT alone may still miss up to 20-25% of CRLM (23).

2.3. Magnetic Resonance Imaging (MRI)

Contrast enhanced MRI gives superior soft tissue contrast compared to CT, allowing

for increased detection of CRLM, and is currently the most accurate modality for assessing CRLM (24). CRLM typically appear as areas of low signal intensity on T1 weighted images and high intensity on T2 images (25). The addition of contrast agents allows for characterization of lesion vascularity and may aide in differentiating benign lesions.

Contrast agents can be either non-specific gadolinium chelates or liver-specific. Liver-specific contrast agents can be divided into hepato-biliary and reticulo-endothelial agents (Table 1).

Table 1.

Type	Agents
Non-specific	Gadopentetate dimeglumine (Magnevist) Gd-DTPA-BMA (Omniscan) Gd-DOTA (Dotarem)
Hepato-biliary	Manganfodipir trisodium (Teslascan) Godobenate dimeglumine (Multihance) Gadoxetic acid (Primovist)
Reticulo-endothelial	Super-paramagnetic Iron Oxide (SPIO)

Non-specific gadolinium chelates are almost entirely passively filtered by the kidneys, and are pharmacokinetically similar to iodinated contrast. SPIO is taken up via Kupffer cells, the spleen and lymph nodes. Despite its high accuracy, hepato-biliary (HPB) agents have been favored over SPIO in clinical practice (26).

HPB agents are taken via hepatocytes and excreted in bile, therefore also delineating the biliary tree. HPB agents are the recommended contrast following neoadjuvant chemotherapy as they allow for the detection of 'disappearing liver metastases', in which CRLM mimic a complete response to chemotherapy (25). Of the HPB agents, Primovist allows for rapid acquisition of dynamic arterial and portal venous phases, not requiring a delay between infusion and scanning.

Sensitivity of Primovist MRI has been reported between 81%-95% (27-29). Contrast enhanced MRI with Primovist offers higher sensitivity than ultrasound and contrast CT scanning in the detection of small liver metastases and for the characterization of equivocal lesions in the liver (29, 30).

The addition of diffusion weighted imaging (DWI) sequences can increase the sensitivity of MRI for CRLM<1cm to as high as 92%, and was shown to be superior to delayed phase contrast enhanced MRI in this regard (27). DWI sequences are now routinely added to liver MRI protocols (25).

2.4. Positron Emission Tomography/Computed Tomography (PET/CT)

There is increasing utilization of PET in the evaluation of potential sites of extra-hepatic disease in patients with suspected liver metastases. The increased uptake of fluoro-2-D-glucose (FDG) in the metabolically overactive malignant cells may aide in the differentiation of equivocal lesions, but may result in false positive findings in areas of inflammatory change.

The role of PET/CT in detecting CRLM is limited, as the sensitivity of PET/CT appears inferior to that of MRI, particularly in the detection of CRLM<10mm, with similar specificity (29-31). A meta-analysis looking at the sensitivity and specificity of PET/CT in the detection of metastatic disease reported rates of 97% and 75% respectively and resulted in a change in management in up to 29% of cases (32). A more recent study reported PET/CT scanning identified lesions missed on contrast enhanced CT in 17% (33).

Therefore, the role of PET/CT scanning may be in the detection of extra-hepatic disease and in cases when the diagnosis in unclear following conventional imaging modalities.

2.5. PET/MRI

PET/MRI is a new hybrid imaging modality that aims to combine the high sensitivity of MRI in detecting small CRLM with the functional data provided by PET. Such devices are restricted to a few highly specialized centres, with insufficient data in the literature.

Current data suggests that the diagnostic performance of PET/MRI is at least comparable to PET/CT in detecting CRLM (25). Lee *et al.* demonstrated that PET/MRI had no significant difference in sensitivity compared to contrast enhanced MRI (34). Nielsen *et al.* utilized PET/MRI in 20 patients following ablative therapy for CRLM, and purposed this modality to improve detection of early disease progression (35).

3. Surgical Resection

3.1. Determinants of Resectability

Traditionally, the following clinicopathological criteria were considered adverse features and as such were exclusions for resection:

- Bilobar disease
- Inability to achieve a 1cm margin
- More than 4 metastases
- More than 5cm in size
- Repeated or multiple resection required
- Extrahepatic disease

There has been a paradigm shift of resectability criteria such that the four main criteria for resection are (36):

- Achievable R0 resection of both intrahepatic and extrahepatic disease
- At least 2 adjacent liver segments spared
- Preserved vascular and biliary inflow and outflow to these remaining segments
- An adequate future liver remnant (FLR) volume (>25% normal parenchyma, >30% impaired liver function)

3.2. Resection margins

Currently there is no consensus on optimal margin width. Most studies have suggested a minimum margin of at least 1mm (37). Cady *et al.* reported an improvement in survival for patients with resection margins of >1cm on univariate analysis (38). The importance of this margin however has been disputed by Pawlik *et al.* who found no significant difference in survival as long as the margins were negative (39). A more recent series by Are *et al*. reported a reduction in median survival from 55% to 42% in patients with negative margins less than 1cm (40). This may be due to the presence of intrahepatic micro-metastases, which are separated from CRLM by a thin rim of liver

parenchyma, but are usually within 1cm of CRLM (36). As expected, R1 or R2 resection was associated with poorer outcomes (39, 40).

Therefore patients should not be excluded on the basis that a 1cm margin cannot be achieved, as a favorable long term outcome can still be achieved with R0 resection.

3.3. Assessment of the Future Liver Remnant (FLR)

The liver volume must be assessed pre-operatively to determine the FLR. Liver function testing and the Childs-Pugh scoring system may identify those at risk of liver failure post resection.

The current gold-standard in quantitative assessment of FLR is volumetric analysis by CT volumetry. In most centres, an accepted FLR in patients with normal hepatic function is between 20-25%, 30% post chemotherapy, and may be as high as 40-50% for patients with chronic liver disease (41, 42).

In patients with compromised liver function such as cirrhotic livers, steatohepatitis and prolonged chemotherapy, a FLR of 40% is considered acceptable (42). In these patients, FLR assessment may not necessarily correlate with liver function (43).

There is some evidence supporting the use of pre-operative assessment of future liver remnant function utilizing the indigocyanine green (ICG) clearance test or ^{99}Tc-Galactosyl human serum albumin (^{99}Tc-GSA) scintigraphy to predict post resection dysfunction (44). A recent study by Hayashi *et al.* demonstrated that functional assessment with ^{99}TC-GSA SPECT-CT identified a further 16% of patients to be safe for resection who were initially classified as borderline function on the basis of volume analysis alone (45). These patients went on to have liver resection and had similar rates of morbidity, mortality and hepatic dysfunction as those patients deemed as having safe FLR on volume analysis alone. This technique may be useful also in the subgroup of patients undergoing portal vein embolisation (PVE) to assess post-treatment future liver remnant function.

3.4. Timing of resection: Colon or Liver first?

Epidemiological studies estimate the rates of synchronous CRLM range from 14% to 25% (44). Metachronous progression occurs in up to 60% of patients (46).

The 3 treatment strategies include: resecting the colonic primary first, resecting the liver metastases first, or a synchronous resection. There is currently no consensus in the literature regarding the optimal approach. Two early meta-analyses have failed to draw firm conclusions regarding the superiority of one approach over another (47, 48). Recently, there has been data to suggest that synchronous resection could be an increasingly viable alternative to staged resections in terms of mortality, morbidity, hospital stay, and disease-free survival (36, 49, 50).

3.4.1. Colon First

Traditionally, the approach to synchronous CRLM would be to resect the primary cancer first for disease source control, followed by hepatic resection several months later (36). This approach allows time for rapidly progressive disease to declare itself, selecting out patients with poor prognosis based on tumour biology (51). A study by Lambert *et al.* reported that 29% patients in their consecutive series were found to have distant disease progression and were hence spared a major hepatic resection (52). This approach is rational in the setting of symptomatic or advanced colorectal primary. The disadvantages of this approach include the morbidity of the colorectal resection and

complications of surgery may delay liver resection and chemotherapy (53). In addition, there is a cumulative morbidity of two major operations.

3.4.2. Liver First

The liver first, or 'reverse approach' is suitable for patients with an asymptomatic primary and CRLM (54). This approach offers the opportunity to control the liver disease early in the course of treatment and prevent the time lost between primary resection and commencement of oncological management (55). Hence this approach may be suitable in patients with CRLM which may be rapidly progressing or borderline in resectability where a delay may render the disease inoperable.

Several studies have demonstrated that patients who underwent a liver-first approach had comparable, if not favorable survival rates compared with the colon-first approach (44, 56).

3.4.3 Synchronous Resection

Some evidence is beginning to emerge in the literature which suggests that simultaneous resection of the primary tumour and CRLM is a reasonable strategy that could spare the patient the burden of undergoing two major procedures, and allow chemotherapy to commence earlier (44).

In a recent meta-analysis performed by Feng *et al.* (49), patients who underwent synchronous resection had significantly shorter hospital stays and had reduced pulmonary complications compared with staged resections. Furthermore, synchronous resections had similar rates of post-operative mortality and long-term survival. However, on subgroup analyses, patients who were selected for synchronous resection had significantly lower numbers of metastases (≤3), and was therefore a major factor contributing to the favorable post-operative morbidity of these patients.

Synchronous resection would be an ideal option in selected patients who are able to tolerate a longer operative time with minimal co-morbidities, have a limited number of CLRM, and who require only a limited colorectal resection (e.g. Right hemicolectomy) (36, 44, 50).

3.5. Other surgical approaches

3.5.1. Portal Vein Embolisation (PVE)

PVE involves the selective cannulation of a branch of the portal vein (typically the right) to induce hypertrophy of the contralateral liver with the aim of increasing the FLR to avoid post resection hepatic insufficiency. Materials used for embolisation includes histoacryl glue, gelfoam, fibrin glue and coils.

The FLR post PVE has been shown to increase by between 8-16% in some series (57, 58). However, there was no demonstrable benefit gained in the series by Farges *et al.* in patients with normal liver function (57). PVE may be considered in patients with normal liver function if undergoing an extended right hemi-hepatectomy (59).

A meta-analysis of 1088 patients found the rate of morbidity for PVE was 2.2% with no mortality. The recorded major morbidities included liver abscesses, cholangitis, haematoma and main or left portal vein thrombosis (60). Hypertrophy of the FLR occurs generally in the first 2 weeks and continues over several months, and delay-to-surgery time is generally at 4-6 weeks (41).

Some concern remains regarding the hypertrophy of liver metastases in the contralateral lobe during the regenerative phase of PVE. However, a recent systematic review showed that PVE did not have any adverse

effect on recurrence rates or OS in patients undergoing major liver resection for CRLM (61).

PVE is hence, a safe procedure used to induce contralateral liver lobe hypertrophy to reduce the rate of post resection liver failure. It renders patients, who would otherwise be unresectable on the basis of their FLR, potential candidates for surgery.

Hepatic vein ligation has been reported in sequence following PVE to induce further hypertrophy of the contralateral lobe. A study by Hwang *et al.* reported an increase in FLR volume at 1 to 2 weeks of nearly 5% over and above that achieved post PVE (62).

3.5.2. Associated Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)

ALPPS is a newer and controversial technique which aims to induce growth of the FLR, and was first described in 2012 (63). ALPPS involves a two-stage liver resection separated by 7 days in which a partial hepatectomy is performed but the diseased lobe is left in situ and ligated, diverting venous blood towards the FLR, therefore allowing for rapid hypertrophy. The second stage is performed within the same admission, which is the metastasectomy of the remnant lobe.

Data on long-term survival is limited. Some studies have cited high post-operative morbidity and mortality, and higher rates of sepsis (64), whilst others have purported to have no mortality (65). This inconsistency in the literature may be explained by a wide variability of technique practiced in different centers worldwide (63).

3.5.3. Two Stage Hepatectomy (TSH)

A two-stage hepatectomy may be required for large bilateral lesions in which complete resection may result in liver failure. The lesser resection is performed first often with portal vein ligation (PVE) of the contralateral lobe to induce hypertrophy of the FLR. The second stage resection is completed 2-3 months later. 20-30% of patients having a TSH do not get to their second operation (59). A recent multi-institutional review of 209 patients who underwent TSH demonstrated a 5.3% mortality rate at 90 days following the second stage, and an overall five-year survival of 45% (66).

3.5.4. Repeat Hepatectomy

Recurrence after hepatic resection is estimated to be more than 60% (59). A study by Wicherts *et al.* reported on 1036 hepatectomies and 28% underwent repeat resections and in 3.8% of patients, up to four resections. Reported post-operative morbidity rates were similar to that of the first resection with 3 and 5 year overall survival (OS) of 76% and 54% respectively (67).

3.5.5. Hilar Lymph Nodes

It is unclear whether surgery and lymphadenectomy of involved hilar nodes is beneficial. Some studies suggest that involved nodes should not represent a contraindication to surgery, however a systematic review identified 15 studies with a total of 145 patients in whom only 5 were alive at 5 years and only 1 was disease free (68).

3.6. Outcomes

The 30-day mortality rate post hepatectomy is between 2.5-6.6% with some referral centres quoting rates as low as 1% (69, 70). A systematic review of surgical resection for CRLMs reported the following rates of complications for hepatic resection (70) (Table 2):

Table 2

Complication	Rate
Wound infection	5.4%
Sepsis	4.6%
Pleural effusion	4.3%
Bile leak	4%
Hepatic abscess	3%
Liver failure	2.8%
Haemorrhage	2.7%

Resection affords 5 year OS rates between 30-60% (8, 46, 71-73) but may be as low as 25%, which was reported in one large series (74). Treatment failures due to recurrences, occur at the liver in 22% of patients and 16% of patients have recurrences in both liver and extra-hepatic sites, with 24% presenting with extra-hepatic disease alone (70).

4. Loco-regional therapies

4.1. Ablative Therapies

Ablative therapies include thermal ablation, radiofrequency and microwave ablation. These therapies are adjuncts to liver resection in patients who would otherwise be unresectable, but do not replace resection as standard treatment (75). Typically smaller lesions are targeted and the larger lesions formally resected for patients in whom complete resection is not feasible.

Radiofrequency ablation (RFA) is performed either percutaneously or operatively via an electrode passed into the lesion. High frequency alternating current creates thermal damage and coagulative necrosis to surround tissue and may be effective up to 7cm diameter, allowing successful ablation of tumours 3-4cm in diameter (59). A limitation specific to RFA is a 'heat sink' effect if the lesion is in close proximity to vessels, rendering the thermal ablation less effective, leading to higher local recurrence rates and vascular injury (75, 76).

Microwave ablation (MWA) can achieve zones of coagulative necrosis approximately 6cm in size and is less susceptible to the heat sink effect. A retrospective matched cohort comparison of MWA to RFA found lower recurrence rates in the MWA group compared with RFA group 6% vs. 20% ($p<0.01$) (77). A Cochrane review identified only one RCT comparing MWA to hepatic resection and demonstrated no difference in outcomes. The review concluded that there was insufficient data to recommend MWA over resectional surgery (78).

Lesions between 1 and 5cm may be treated, although 3cm appears to be the ideal diameter for ablative therapy. A small retrospective series of 67 consecutive patients found local recurrence rates post liver resection to be 10.4%, and post RFA to be 66.7%. However, in CRLM <3cm the local recurrence rates were equal to those patients undergoing resection (79).

Ablative modalities are not recommended for lesions located near blood vessels or the diaphragm due to the risk of perforation (80). Other complications include haemorrhage, thermal injury to other structures, tumour seeding and infection. The post-ablation mortality rate has been suggested

at 0.5%. Recurrence rates are lesion size dependent with 33% recurrence in CRLM > 3cm (81).

CRLM which may be suitable for ablation are those deemed unresectable due to a difficult location or inadequate liver function and centrally located lesions 1-2cm (82).

4.2. Selective Internal Radiation Therapy (SIRT) Spheres

SIRT is performed using resin microspheres of Yttrium-90 emitting beta radiation, introduced via the hepatic artery. This method induces parenchymal atrophy as well as tumour necrosis. It also results in hypertrophy of the non-tumour bearing liver. Its role is largely in the treatment of non-resectable liver lesions. A Cochrane review published in 2009 identified only two randomised control trials (RCT), one with 21 patients comparing SIRT and chemotherapy to chemotherapy alone (5-fluorouracil (5-FU)/ Folinic acid), which found the addition of SIRT almost doubled progression free (11.4 vs. 4.6 months) and OS (29.4 vs. 11.8 months) times (83). This chemotherapy regimen no longer reflects standard of care and the study numbers are small so firm conclusions cannot be drawn.

More recently, the addition of SIRT to a modified FOLFOX chemotherapy regimen was assessed in the SIRFLOX trial, a phase III RCT. Whilst the addition of SIRT decreased disease progression in the liver by 30%, it did not affect overall progression free survival, or liver resection rates (84).

As such, there is currently a paucity of evidence regarding SIRT in improving OS in patients with CRLM (85). Therefore, results from future phase III RCTs, such as the FOXFIRE trial comparing the addition of SIRT to 5-fluorouracil, oxaliplatin and folinic acid (86) will be keenly awaited.

5. Chemotherapy

The following agents form the backbone of modern chemotherapy for colorectal cancer (Table 3).

Table 3

Class	Agents	Side effects
Fluoropyrimidines	5-FU Capecitabine (pro-drug of 5-FU)	GI toxicity, hand foot syndrome, rarely coronary vasospasm
Platinum derivatives	Oxaliplatin	Thrombocytopaenia, peripheral sensory neuropathy
Topoisomerase inhibitor	Irinotecan	GI toxicity, neutropaenia
VEGF inhibitors	Bevacizumab (Avastin) Aflibercept (Zaltrap)	Hypertension, GI bleeding and perforation, nasal septum perforation
EGFR inhibitors	Cetuximab (Erbitux) Panitumumab (Vectibix)	Rash, photosensitivity, hypotension

The combinations used include FOLFOX (5-FU, Folinic acid and Oxaliplatin), XELOX (Capecitabine and Oxaliplatin) and FOLFIRI (5-FU, Folinic acid and Irinotecan).

5.1. Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy for resectable CRLM allows early treatment of the micrometastatic disease, downsizing the tumour to potentially improve the rate of R0 resection, and also allow patients with poor tumour biology to declare themselves (36).

The EPOC study randomised patients in 6 cycles of FOLFOX neoadjuvant chemotherapy followed by surgery vs. surgery alone. There was a significant difference in progression free survival in the neoadjuvant chemotherapy arm of the trial (36.2% vs. 28.1%) at 3 years (87). However, OS was no different in long-term follow-up of the same study although the study was not powered to detect this (88). Adam et al reported a 5 year survival of 33% in patients successfully downsized after chemotherapy and underwent resection (89).

In current practice, it is widely accepted that patients with resectable CRLM should receive neoadjuvant chemotherapy (36). However, no clinical trial to date has shown that this practice would prolong OS (90). Due to the lack of clear evidence, it has been suggested to limit chemotherapy to 6 cycles to limit substantial associated side effects such as chemotherapy associated liver injury (44).

5.2. Chemotherapy Associated Liver Injury

A drawback of neoadjuvant chemotherapy is the condition of chemotherapy-associated steatohepatitis (CASH) which is becoming more common. Irinotecan has been associated with steatohepatitis, which may progress to fibrosis/cirrhosis and has been shown to increase the 90 day mortality (14% vs. 2%) (91).

Agents such as oxaliplatin are associated with sinusoidal dilatation leading to a condition referred to as ‘blue liver’ which refers to the sinusoidal dilatation leading to injury and poorer liver function. One study found up to 79% of patients treated with oxaliplatin had evidence of sinusoidal damage vs. 23% in patients who did have oxaliplatin (92).

Given this risk of toxicity and increased complication rates, the timing of hepatic surgery and chemotherapy is critical. Welsh *et al.* reported increased complication rates if patients had been on chemotherapy for more than 12 weeks, or if they have been off chemotherapy for less than 4 weeks prior to surgery (93).

5.3. Adjuvant Chemotherapy

Adjuvant chemotherapy following liver resection is recommended, and has been shown to increase disease-free survival (DFS) (94). Portier *et al.* demonstrated in a RCT that adjuvant chemotherapy with 5-FU/Folinic acid increased five-year DFS to 33.5%, compared to 26.7% in patients who underwent surgery alone (95).

There is currently no consensus in regards which regimen is optimal for adjuvant chemotherapy (96). A recent RCT compared FOLFIRI to 5-FU/Folinic acid in 309 patients following liver resection, and found no significant difference between the two regimens in terms of DFS or OS, although the FOLFIRI group experienced more adverse effects (97).

5.4. Chemotherapy in unresectable CRLM

Chemotherapy regimens in CRLM are now achieving high response rates (>50%) and long median survival times (up to 30 months) (36). A regimen of FOLFOX plus

irinotecan (FOLFOXIRI) has been reported to have response rates of 70.4% with almost of fifth of patients achieving R0 liver resection. OS at five years was 42% (98).

The role of monoclonal antibody agents remain an area of intense research. Several RCTs comparing the addition of cetuximab or bevacimab have not demonstrated significant difference, with both recommended as additions to FOLFOXIRI as first-line therapy (99, 100).

Second-line therapy with FOLFIRI plus panitumumab has been suggested (101).

Up to 75% of patients with CRLM present with unresectable disease (36). With chemotherapy, 10-20% of these patients may be converted to resectable disease (102, 103). Survival in these patients was reported at 33% at 5 years and 23% at 10 years (103).

Optimal timing for assessment of response to chemotherapy has been suggested at every 2 months (36).

5.5 Hepatic Arterial Chemotherapy (HAC)

The rationale for hepatic arterial infusion of chemotherapy is that metastases in the liver derive their blood supply from the hepatic artery rather than the portal vein. A Cochrane meta-analysis identified 7 RCT's and reported no difference between the HAC and standard therapy and a trend to poorer OS in the HAC group. As a result it is not a recommended therapy at this time (104).

6. Conclusion

Liver resection has progressed a long way since Cattell reported on the first successful removal of liver metastases in 1940 (105). Patients undergoing liver resection for CRLMs have far superior outcomes to those having chemotherapy alone with 5 year overall survival in some series as high as 50-60% (11). The approach to investigation and management of CRLM remains a complex area in which practice is continuing to evolve with new evidence, and which ongoing research is required.

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