



Current Management of Colorectal Cancer with Liver Metastasis

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Abstract

Colorectal cancer is a worldwide public health problem. More than 20% of patients with colorectal cancer present at an advanced stage, and the liver is the most common site of metastases. More recently, selection criteria for resectability have been expanded, but definition of resectability still remains challenging. Since the presence of metastases is the most relevant prognostic factor, surgical resection of liver metastases is the mainstay of treatment. The most appropriate resection approach remains controversial, but both staged and simultaneous resection has been shown to have comparable survival advantages and long-term outcomes. The advent of new chemotherapeutic agents and the development of loco-regional therapies (embolization, ablation, and infusion chemotherapy) have contributed to better outcomes. It is deemed reasonable to adopt combination therapy for unresectable metastases. In view of the lack of standardized evidence-based protocols, optimal management of hepatic metastases should be individualized to the single patient and decided through a multidisciplinary approach. Early detection is always the ultimate goal to reduce metastatic colorectal cancer burden worldwide. In this overview, the current management of liver metastases originating from colorectal cancer is presented.

Keywords: Colorectal cancer; Liver metastases; Liver resection; Hepatic resection; CRLM

Introduction

Colorectal cancer (CRC) is an increasingly global health issue [1]. According to the most recent epidemiological data, it accounts for more than 1.4 million newly diagnosed cases each year [2]. CRC is the most common gastrointestinal tumor and the third most frequently diagnosed malignancy in men and women worldwide, however, there is a wide geographical variation in incidence and mortality [1-3]. Liver is the most common site of distant metastases from CRC [4]. More than 50% of patients will develop liver metastases sometime in the course of their disease; in addition, presentation of liver metastases at the time of diagnosis (stage IV disease) is reported in 15 to 20% of cases [5]. Traditionally, patients with metastatic liver disease were deemed inoperable; however, surgical resection for liver metastases has more recently been shown possibility to achieve cure or prolong survival [5]. In fact, recent modifications of resectability criteria for liver metastasis have significantly improved outcomes with five-year and ten-year survival rates reaching up to 40% and 25% respectively [6,7]. However, 1-year recurrence rate after metastases resection has been reported in up to 30% of cases [7]. When surgical treatment of liver metastases is not feasible, chemotherapy, radiation therapy and/or ablation techniques can be used with satisfactory outcomes [8]. This review examines the current management of colorectal cancer with liver metastases (CRLM). Comments about effectiveness, complications as well as survival benefits are discussed.

Perioperative evaluation

In order to minimize postoperative complications, perioperative assessment of patient's fitness for surgery and liver status are crucial. Presence of co-morbidities and patient's performance must be carefully assessed as these affect resection outcomes and treatment plan through a dedicated multidisciplinary team. Comprehensive blood investigations should be routinely obtained before surgical resection including liver function tests, coagulation profile, bilirubin, creatinine and carcinoembryonic antigen (CEA) [9]. The 'Patient Safety in Surgery Study' has highlighted that advanced age, male gender, low serum albumin, presence of underlying liver disease (hepatitis or alcoholic hepatitis), ascites, kidney failure, bleeding disorders, cardiomyopathy, and chronic obstructive pulmonary disease are associated with substantial morbidity and mortality following liver resection [10].

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Radiological evaluation

Radiological assessment of CRLM is mandatory to plan surgical resection [11]. The three main radiological modalities to evaluate CRLM as well as extra-hepatic disease (EHD) are: computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan [11]. Hepatic metastases are easily detected as hypoattenuating lesions using contrast-enhanced CT scan with 85% sensitivity rate in most references [11-14]. However, a higher detection rate (reaching up to 90%) can be obtained using contrast-enhanced multi-detector CT scan [13]. In cases of underlying liver disease (steatosis, cirrhosis), following chemotherapy, or to identify sub-centimetric lesions, MRI with liver-specific contrast agents is superior to CT scan with more than 90% sensitivity [14].

Specificity of the three diagnostic modalities is high and has been reported as 95%, 93%, and 97% for CT, MRI and PET CT respectively [15]. PET scan is used to obtain whole body map to identify EHD that could rule out liver resection [15]. A recent meta-analysis has shown FDG PET scan to be the best radiological modality for detection of liver lesions from gastrointestinal origin [16]. Moreover, adding CT to FDG PET improves sensitivity up to 97% [15]. In patients with recent chemotherapy treatment PET scan has high false-negative rates [17]. More recently, intra-operative ultrasound (IOUS) has been increasingly used in surgical practice. It is safe, inexpensive and a very useful adjunct to preoperative investigations, being able to detect new lesions in up to 20% of cases [18].

Current Treatment Strategies

Chemotherapy

Neo-adjuvant Chemotherapy for Resectable CRLM: The use of neoadjuvant chemotherapy in resectable CRLM is still controversial [19]. Many authors claim that upfront induction chemotherapy has many advantages. ¹⁹In fact, it can assess tumor sensitivity, downstage large or multiple liver lesions leading to easier resection, and more importantly may treat potential micrometastases [19]. However, a potential drawback of induction chemotherapy includes possibility of delayed surgical treatment for a subset of patients in whom disease will continue to progress [19,20]. Also, chemotherapy carries a substantial risk of hepatic toxicity with steatohepatitis that is associated with increased 90-day postoperative mortality [21]. In addition, it can make liver metastases undetectable on preoperative imaging, a relatively new clinical problem that can be seen in 5-25% of patients with the use of current chemotherapy agents [22]. In a recent multicentric randomized trial comparing surgery alone to perioperative chemotherapy (6 cycles of preoperative and post operatively of FOLFOX4) in a cohort of 364 patients with initially resectable CRLM, no major differences were found in five-year overall survival between both groups (48% in the surgery-alone group versus 51% in the perioperative chemotherapy group) [23]. However, there was an absolute increase of 7.3% in the rate of progression-free survival (PFS) at 3 years in the perioperative chemotherapy group [23].

In current practice, it is widely acceptable that patients with resectable CRLM receive perioperative chemotherapy; however, no clinical trial has shown that this practice would prolong overall survival (OS) [24]. Due to the lack of clear evidence of overall survival improvement with chemotherapy, it has been suggested to limit chemotherapy to 6 cycles given for no longer than 3 month due to the substantial associated side effects [25], especially when a major hepatectomy is needed [26].

Adjuvant Chemotherapy for Resectable CRLM: The ultimate dilemma after complete CRLM resection is the rate of recurrence that is reported as high as 70% after complete surgical excision. Unlike neoadjuvant treatment, several studies have shown benefit of adjuvant chemotherapy in terms of longer disease-free-survival (DFS) [27]. More than one study has demonstrated that that use of adjuvant chemotherapy FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) after liver resection is superior to liver resection alone [28]. A recent meta-analysis has shown that adjuvant chemotherapy is associated with longer OS when compared to surgery alone, although the difference has not been found to be statistically significant [29]. The classic four chemotherapeutic agents studied as adjuvant treatment are: 5-fluorouracil/leucovorin (5-FU/LV), capecitabine (the oral fluoropyrimidine carbamate), oxaliplatin and irinotecan [30,31]. More recently, molecular-targeted agents including anti-angiogenic drugs (bevacizumab, regorafenib and aflibercept) and anti-epidermal growth factor receptors agents (anti-EGFR), such as cetuximab and panitumumab, have been introduced in the market [30,31].

Generally, adjuvant chemotherapy after resection of metastases is highly recommended, however the best regimen protocol remains controversial [29]. There is also a lack of consensus about the impact of adjuvant chemotherapy on OS in the setting of resectable CRLM [28]. The National Comprehensive Cancer Network (NCCN) guidelines accredited more than one chemotherapy line [30,31]. According to most trials, 5-fluorouracil/leucovorin (5-FU/LV) with or without oxaliplatin remains the recommended first-line [28]. However, during the last few decades, a trend into combination therapy has emerged and more than one combination has been investigated. A recent trial has identified no significant difference in OS and median DFS when FOLFIRI (5-fluorouracil/leucovorin and irinotecan) and 5FU/LV (5-fluorouracil/ leucovorin) administered after complete resection of CRLM, were compared (22 months for the 5FUILV group vs. 25 months for the FOLFIRI group). However, a trend was observed for improved DFS in the patients receiving FOLFIRI. Additionally, grade 3/4 toxic side effects were more common in the FOLFIRI group (47% vs. 30%) [32].

Chemotherapy for Unresectable CRLM: About 80% of patients with CRLM have unresectable disease at the time of presentation [33]. This group of patients has complex disease, and therefore may require a combination of loco-regional therapy regimens including ablation, embolization or radiation. However, systemic chemotherapy is the mainstay of treatment and several lines known to have good response rate are available [30,31]. In a recent study, infusional 5FU/LV, oxaliplatin an irinotecan (FOLFOXIRI) followed by surgical resection has been shown to be associated with a high response rate (70.4%) with 19% of patients achieving an R0 surgical resection. OS at 5 years and 8 years were reported as 42% and 33% respectively. At 5 years, 29% of patients were disease free [34]. Conversion rates of unresectable disease to resectable differ in the literature ranging from 5% to 38%. This variation in final outcomes is due to several factors including disease extent, type and duration of chemotherapy treatment [35]. Failed response to first line chemotherapy is an extremely poor prognostic factor. In fact, best response rate after second line chemotherapy does not exceed 10% [35].

The use of anti-EGFR and anti-vascular endothelial growth factors (anti-VEGF) is becoming more common in cases of unresectable metastases [36]. However, various studies have identified only a slight

gain in response rate when bevacizumab is added to FOLFOXIRI (fluorouracil - leucovorin, oxaliplatin, and irinotecan) as first line chemotherapy regimen [36].

Surgical Excision of Metastases

Surgery is the mainstay of treatment for liver metastases from colorectal cancers, and can provide up to 55% five-year survival [37]. Metastases are not considered a contraindication to surgery if excision of all metastatic deposits can be achieved with an adequate future liver remnant (FLR) [38].

Criteria for resectability

There has been a paradigm shift in the CRLM resectability criteria over the last few decades [6]. In fact, criteria have expanded and they are less dependent on the presence, number, size and location of the lesions; in addition, more emphasis has been placed on the volume and function of the future liver remnant (FLR) rather than the extent of resection [25]. The presence of EHD is currently no longer considered to be a contraindication [6]. Currently, the minimum requirements needed prior to resection of liver metastases are: 1) Achieving an R0 resection of both intrahepatic as well as EHD. 2) At least two adjacent liver segments should be spared with blood and bile inflow and outflow preservation 3) Adequate future remnant liver volume and function (at least 25% estimated normal liver parenchyma and 30% in case of impaired liver function tests) [27,39,40].

Timing of colon and Liver resection

The sequence and best timing of CRLM resection is still controversial and several approaches have been proposed, especially with chemotherapy being increasingly used. Strong evidence is still lacking and there is no randomized controlled trial comparing different methods [41,42].

There are several approaches described in the surgical literature. The classic surgical approach is “primary first” in which resection of the primary colorectal cancer is followed by chemotherapy and eventually by resection of metastases after 3 to 6 months. This staged resection is best for patients with significant co-morbidities, symptomatic colorectal cancers, inadequate FLR, and advanced primary cancer. In fact, when the tumor is advanced, a higher complication rate may be observed during chemotherapy, and there is possibility of progression of disease leading to inoperability [41]. Another main advantage of this approach is to identify patients with occult liver metastases that may become detectable during adjuvant chemotherapy avoiding the morbidity of a liver resection [42]. However, some patients might experience progression of liver disease especially if delays are encountered due to complications after resection of the primary [41,42]. The other approach is the simultaneous resection of liver metastases and primary tumor. This approach avoids delays in treatment since all cancerous lesions are removed in one single procedure and chemotherapy treatment can be started earlier if no complications occur. However, increased postoperative morbidity and mortality due to bacterial contamination of the surgical field is a potential issue that should be taken into consideration [43]. This approach suits best colon cancers and single group of patients who can tolerate longer operative times [8]. The third known approach is the alternative staged “liver-first” approach. This approach consists of liver metastases resection (usually following 3 to 6 cycles of systemic chemotherapy) followed by resection of the colorectal tumor (adjuvant chemotherapy might be given in between both procedure). Recent data showed that liver-first approach is

better for selected patients with advanced CRLM when chemotherapy might provide better results if given before [44].

Extra-Hepatic Disease (EHD)

The presence of EHD is associated with a poor prognosis [45]. Lungs are the second most common sites of metastases (after lymph nodes) from CRC, followed by the peritoneum, brain and bone [45]. EHD is no longer a contraindication to surgery [6]. Recent reports show longer DFS and five-year-survival rates in patients with resection of pulmonary metastases compared to those receiving chemotherapy alone [7].

Regarding lymph nodes involvement, the OS following resection of specific groups of lymph nodes differs according to site and number [46]. In fact, worse outcomes have been reported after resection of aortocaval or celiac lymph nodes compared to hepatic pedicle nodes. Similarly, the higher the number of lymph nodes involved, the poorer the outcome [46]. However, when the median survival of individuals with chest lymph nodes involvement were compared, intra-thoracic metastases found to have better five-year-survival than mediastinal ones [47].

Other surgical approaches

FLR is the utmost limiting factor to perform major hepatectomies. Therefore, surgeons have developed innovative techniques to accelerate liver growth in order to increase resectability. Those strategies include (but not limited to), Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) and two-stage hepatectomy (TSH).

ALPPS is one of the main novel techniques in recent years. ALPPS was first described in 2012 to achieve sufficient hypertrophy prior to major hepatectomy [47]. The main idea is to divert the venous blood flow away from the lobe where tumor is located with portal vein ligation to induce hypertrophy in the contralateral lobe, then to resect the tumor-bearing lobe. Use of ALPPS, indications, and safety is still a controversial among hepatobiliary surgeons [48]. Some centers reported high morbidity and mortality reaching up to 30%, in opposite to that, several studies demonstrated ALPPS to achieve up to 90% increase in the FLR [49-51]. Due to this huge variability in long-term outcomes and lack of standardization, we cannot draw firm conclusions if ALPPS is to be considered a treatment choice for marginally resectable or initially non-resectable CRLM. The other relatively new surgical procedure is TSH. To date, TSH is the standard of care for extensive CRLM. It has been found that TSH significantly improved resectability rates (up to 50%) but associated with high rates of drop out (up to 30%) after the first procedure due to disease progression remains a concern [52]. Therefore, Trozilli G. et al. [53] encouraged one-stage hepatectomy (OSH) approach with no local recurrence in a median follow up of 14 months. Clearly, this short median follow up time precludes any conclusions regarding the safety and feasibility of OSH for extensive CRLM. More recently, laparoscopic approach was examined in TSH and found to be safe and feasible by Fuks D. and his colleagues [54]. In regard to 90-days mortality of TSH in comparison to ALPPS, Adam R. et al. [55] reported higher 90-days mortality with ALPPS approach in a propensity matching score analysis of 58 patients with multiple liver metastases.

Loco-Regional Therapies

Over the last several decades, more patients with unresectable

CRLM at presentation are being treated with ablative techniques with good outcomes. In addition to chemotherapy, they have been shown to prolong OS by approximately 20 months in comparison to chemotherapy alone [56,57]. Selection of the best loco-regional treatment has to be tailored to every case through a multidisciplinary approach [57].

Ablation techniques

Radiofrequency ablation (RFA) is a widely used form of ablation allowing application of extreme temperature for ablation of the tumor with minimal toxicity to the surrounding liver parenchyma. Published data show low toxicity rates, less than 1% mortality and less than 10% morbidity regardless of the route of administration [58]. The “heat sink effect” remains a major downside of RFA with possibility of significant hepatic or vascular injury [59]. Hence, RFA is not recommended for unresectable lesions, lesions located near blood vessels or diaphragm due to the substantial risk of perforation [60]. Another limitation of RFA is the recurrence rate especially with lesions higher than 3 cm or if it was delivered percutaneously [61]. External Beam Radiation (EBRT) using high frequency microwave radiation is another modern technique, which causes coagulation and necrosis of the tumor deposits. This technique is not well studied and there are concerns about its safety [62]. One of the largest series reported a 6% local recurrence rate [63]. The potential role of EBRT has increased over the years with advances in imaging techniques [63]. Due to its low therapeutic window, toxicity remains a major concern. However, for liver tumors in general and in selected patients, EBRT has shown to be safe and effective as a loco-regional treatment modality [57]. A dose of 60 Gy (gray) for local disease control has been reported to be a safe [57]. In light of the limitation of the RFA and EBRT, a newer technique has been used emerged in the field. The Irreversible electroporation (IRE) uses a Nano-knife to deliver high-voltage electricity directly to the tumor to induce cell death under radiological control. Since IRE is a non-thermal technique, the area of ablation will not suffer from ‘heat-sink effect’; therefore, IRE is relatively safe for metastases close to vital structure [64]. Short-term response rate is about 50% and was associated with lesions < 1 cm [65,66] and the lowest effectiveness was associated with tumors of colorectal origin [67]. IRE uses high velocity of electrol pulses; so, it has to be performed under general anesthesia and patients need to be monitored not to develop cardiac arrhythmias [64]. To our knowledge, COLDFIRE-2 is the only one single-arm phase II clinical trial that has been done to assess the efficacy of IRE to treat CRLM. It showed that IRE is a promising modality of treatment with good safety index for the difficult to reach lesions [68]. At this time of development, there are no studies comparing IRE to other ablation techniques. Likewise, there are many questions unanswered about IRE in the treatment of CRLM, therefore, larger prospective clinical research is needed [66].

Embolic intra-arterial therapies

As a new liver-directed locoregional technique, they showed sufficient control of liver metastases in first and later lines of patients with CRLM. In comparison to the systemic chemotherapy regimens offered to patients with CRLM, they were found to be superior to systemic chemotherapy in hepatic PFS. Trans-arterial chemoembolization in general offered higher concentration of the chemotherapy agent than the infusion route. To date, there is no consensus on what is the standard protocol for chemoembolization but varies between centers [69]. Trans-Arterial Chemoembolization

(TACE) has serious complications like ‘tumor-lysis syndrome’ and ‘post-embolization syndrome’; both are self-limiting and resolve within short period of time [70]. Due to median survival benefits (8 to 12 months) of TACE, it will remain a preferable treatment option for unresectable CRLM, provided a preserved liver function however, different strategies of chemoembolization need further prospective studies [71]. More recently, there is growing literature supporting the use of TACE along with the drug-eluting beads with irinotecan (DEBIRI). It has been found to have a longer overall survival (7 months) when compared to systemic FOLFIRI in a phase III randomized trial [72]. Furthermore, can down stage non-resectable metastases when combined with first-line systemic chemotherapy (FOLFOX), however, a technical aspect of the procedure is still debated [73]. Selective Intra-arterial radiation therapy (SIRT) is another intra-arterial embolic treatment for CRLM. There is a sufficient body of evidence indicating that SIRT is a safe, however, some authors reported serious hematological and gastrointestinal complications, such as bleeding, radiation induced cholecystitis or radiation-induced liver disease [74]. SIRT uses yttrium-90 (⁹⁰Y) bound to resin microspheres to be injected into the metastatic lesion through the hepatic artery. In a randomized phase III control trial for patients with liver-limited metastatic lesions who have failed chemotherapy, Hendlisz A. et al. [75] compared fluorouracil infusion versus radio-embolization against intravenous fluorouracil and found a prolonged time to tumor progression in the radio-embolization arm. Furthermore, SIRFLOX-study showed around 30% decreases in disease progression in the liver when SIRT using ⁹⁰Y is added to Folfox as a first line chemotherapy [76]. Also, in a recent review of the current evidence by Townsend A. et al. [77] SIRT showed neither survival benefit nor a better quality of life. Clearly, majority of studies showed either tumor response or slowing down tumor progression [78]. To date, there are four randomized clinical trials comparing the effectiveness of SIRT with chemotherapy to chemotherapy alone, none examined OS [65]. Therefore, data of OS from SIRFLOX combined with FOXFIRE and FOXFIRE Global will be necessary before implementation into standard practice.

Conclusions

Recent advances in the treatment of metastatic colorectal liver disease have allowed expansion of resectability criteria with an increased number of patients being cured or living with better disease control. There is currently no consensus regarding the sequence of surgical resection of the primary cancer and metastatic disease. However, the use of neoadjuvant chemotherapy is generally accepted as a primary step. Surgical resection is feasible as long as complete removal of cancer is achievable and adequate residual functioning liver parenchyma is preserved. Adjuvant chemotherapy is highly recommended, though protocols are not yet well standardized. In case of unresectable disease, combination chemotherapy treatment may induce regression of disease and allow for possibility of resection and cure. In the battle against liver metastases from colorectal origin, loco-regional treatments are gaining more support and may achieve good local control, however, not recommended as first-line treatment options for resectable metastases. For all patient with liver metastases, a multidisciplinary approach is to be emphasized for optimal management and an individualized evidence-based approach must be adopted to achieve best clinical and survival outcomes.

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