

Local and Systemic Treatment of Potentially Resectable Colorectal Liver Metastases

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Received date: Mar 20, 2014, Accepted date: May 24, 2014, Published date: May 31, 2014

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Abstract

Advances in surgical fields and chemotherapy regimens have been increasing long-term outcomes for patients with Colorectal Liver Metastases (CRLM). The liver resection remains the main treatment for resectable CRLM, but the progress of the chemotherapy regimens has been changing the oncologic approach for those patients who present unresectable liver disease treated with chemotherapy who reach tumor shrinkage allowing hepatic resection. Looking for potentially resectable CRLM, it seems that chemotherapy should always be offered as additional treatment to curative-intention liver resections, increasing Recurrence Free Survival (RFS), but not affecting Overall Survival (OS). The optimal timing for each chemotherapy regimen has not been answered by Randomized Clinical Trials (RCT) yet. Retrospective series are biased on different patient selection for different chemo modalities. The best candidate for each regimen of chemotherapy could not yet be defined, but clearly patients with more aggressive disease were preferred to preoperative chemo regimens testing chemo responsiveness and selecting "good responders" before surgery. These patient selection criteria have not been standardized yet but the rationale of additional chemotherapy, regardless the timing of administration, has been assumed as stand of care for patients who underwent curative-intent resection. The main objective of this review was to collect information to be taken in consideration for different approaches in the management of CRLM.

Keywords: Colorectal liver metastases, Surgery; Chemotherapy; Long-term outcomes

Introduction

Colorectal cancer (CRC) represents the third most common malignancy in the United States with 136,830 of estimated new cases and 50,310 expected deaths in 2014 [1]. Although these numbers represent high incidence of colorectal cancer, they also represent decreasing of rates (around 4%) when compared with the recently years (2008-2010) [1]. The screening with colonoscopy has been considered the main responsible for it [2-4]. In general, the last 25 years were vital to the progress of CRC treatment, mainly for advanced diseases. Colorectal Liver Metastases (CRLM) is present in 15–20% of patients at the time of diagnosis and develops in another 60% of patients during the course of the disease [5]. CRLM are the most common indication of hepatectomy in Western countries, since improved comprehension of liver anatomy, refinements in surgical technologies, improved imaging techniques, better post-operative care and new systemic chemotherapy made the surgical management of the CRLM possible [6-11]. Moreover, the use of additional chemotherapy in these patients has been reducing Recurrence Free Survival (RFS), however with no differences in Overall Survival (OS) [10-12]. Whether these agents should be given before hepatic resection or only after surgery remains as an open debate and the purpose of this review is to highlight aspects that should be considered to make decisions about the appropriated timing for systemic and surgical treatment of potentially resectable CRLM.

Natural History and Patient Selection

The natural history of CRC had been studied and reported with no survival in 5 years survivors for CRLM whose did not underwent complete resection [13,14]. Based on patients who underwent surgical treatment, clinical risk scores estimating the risk of recurrence and prognosis in patients with CRLM have been published [15,16]. Fong et al. described a Clinical Risk Score (CRS) for predicting recurrence after hepatic resection for metastatic CRLM describing one thousand and one patients population, and it became one of the most used clinical risk score for recurrence [16]. All criteria described in this clinical risk score can be available in pre-operative evaluation. The clinical criteria consisted of: nodal status of primary, disease-free interval from the primary to discovery of the liver metastases of <12 months, number of tumors >1, preoperative CEA level > 200 ng/ml, and size of the largest tumor >5 cm were chosen as the criteria for a clinical risk score. Each criterion was assigned one point and the total score was compared with the clinical outcome of each patient before liver resection. Patients with scores of 0, 1 or 2 have a highly favorable outcome and surgical resection is a rational therapy for this group. Patients with scores of 3 or 4 have a worse prognosis and the authors recommended that resection should be planned in the context of adjuvant therapies. Patients with a score of 5 have very poor outcomes and resection without additional effective adjuvant therapy or outside of adjuvant trials would be considered highly questionable. In this study, overall survival of patients was 37% in five years and the median survival was 42 months [16].

In early 1990, extrahepatic metastatic disease (EHMD) had been considered a contraindication to resection of LM, mainly because of low reported 5-year survival rates in these patients [17]. However,

Elias et al. reported that the 5-year survival rate of hepatectomy with the simultaneous resection of extrahepatic disease with curative intent was 29% [18,19]. In 2001, Adam et al. published a study that showed a 5-year survival of 36% in those patients with resectable EHMD treated and resected CRLM [20].

The most common site of EHMD in CRC is the lung [21]. Lung metastasectomies for CRC in selected patients with CRLM is considered beneficial and is associated with a 5-year survival rate of around 40% [22,23]. Carpizo et al. studied 127 patients with concurrent resection of CRLM and EHMD [24]. The 3 and 5-year survival rates for patients with concomitant EHMD were 47% and 26%, respectively, compared with 67% and 49% for those without EHMD ($p > 0.001$). The use of pre-operative chemotherapy could help in the evaluation of responsiveness during the selection of patients with EHMD, with potentially resectable lesions. The selection of patients who undergo resection would be based on their response or with the progress of disease in use of chemotherapy. Although, the control of EHMD should be considered in select cases, the role of hilar and retroperitoneal lymphadenectomy is still unclear. The hilar lymphadenectomy could provide a more accurate prognosis and avoid obstructive jaundice in the future, but makes the future surgical approach difficult [22]. The retroperitoneal lymphadenectomy should be avoided in front of high morbidity and worse prognosis [21,22].

The improved efficacy of chemotherapy agents has not only allowed increased long term outcomes, in the non-curative setting, but has allowed a subset of previously unsusceptible patients treated with chemotherapy undergoing hepatectomy after tumor shrinkage or consolidating therapy after curative resection. But the decision about the appropriated timing for chemotherapy in the curative-intent surgical treatment of CRLM remains unclear.

Surgical Approach

The hepatectomies for CRLM has been proved as potentially curative treatment since the mid 90's [25,26]. Patients with metachronous CRLM, stable or low progress disease and favorable anatomic position have clear indication of surgery and adjuvant chemotherapy. But the best timing for surgery in patients with synchronous, multiple or bilobar disease remains controversial. For patients with initially unsusceptible disease, the inclusions in institutional protocols or individual conducts have been made. Many efforts have been made to increase the number of patients who could obtain benefits with hepatic resection: refining prognostic factors that would improve patient selection; advancements in surgical technique such as, use of intraoperative ultrasonography, controlling hemorrhage through use of vascular clamping techniques supplemented with low central venous pressure anesthesia, availability of novel devices for parenchymal transection, and controlled anatomic hepatectomy; and novel approaches to permit curative hepatic resection such as, preoperative portal vein embolization for hypertrophy of future liver remnant, ablation techniques and staged hepatic resection [27-32].

Concerning major hepatectomies, the remnant liver volume is always a true concern to avoid postoperative liver failure [33,34]. The portal vein embolization of one side of the liver could produce hypertrophy of the contralateral side, enabling the surgeon to safely spare a portion of the liver enough to provide normal liver function. To decide whether the embolization is necessary, an estimation of the remaining liver volume has to be performed. Generally, 30% of the

liver needs to remain after surgery, but this amount may have to be increased if there is liver damage from chemotherapy or cirrhosis. There are many options of ablative techniques, including cryosurgery, microwave and Radiofrequency Ablation (RFA), which can be done percutaneous guided-imaging or intraoperative when disease cannot be suspected. In a retrospective series comparing 418 patients treated with resection only, RFA and resection and RFA alone, recurrences were lowest with resection only (52, 64 and 84%, respectively) [27]. However, the reasons why patients received RFA instead of resection are usually based on more extensive disease that cannot be encompassed by resection. Predictors of better survival with RFA include a lesion of less than 3 cm, a lower baseline CEA value and less than three lesions [28]. The location of the lesion is also important since adjacent tumors to large vessels being difficult to ablate because of the intrinsic cooling provided by blood flow in the vessel [5]. The complications coming from technical challenges are intraoperative bile ducts progressing to post-treatment stenosis and risk of bleeding after rupture of liver capsule for peripheral lesions.

Adam et al. modified the paradigm of an incomplete resection should not be indicated [28]. They have reported an alternative strategy that consisted of planned two-staged resection in 13 patients where the initial resection removed the highest number of metastases as possible, followed by chemotherapy to limit residual tumor growth while the remnant liver hypertrophies after portal vein embolization. When adequate parenchymal hypertrophy has occurred, to avoid hepatic failure and after documenting absence of disease progression, the patient undergoes a second hepatectomy. With such an approach they achieved a 3-year survival rate of 35%, a median survival of 31 months and 44 months, from the second hepatectomy and from the time of initial diagnosis of metastases, respectively. The authors admit that patient selection is critical, and the group that underwent two-stage procedures represented only 27% of the patients with bilobar tumors [28]. An alternative staged-approach was proposed by Kianmanesh et al. for patients with multiple bilateral metastases where the first stage involves clearing the left liver of metastases by local resection and concomitantly performing a right portal vein ligation [35]. The second stage includes a right hepatectomy after hypertrophy of the cleared left liver, usually through a different abdominal approach. The objective of the first hepatectomy is to make the second hepatectomy potentially curative. The timing of the second hepatectomy is selected as a function of liver regeneration, control of remnant liver tumor by chemotherapy, and the probability that the second hepatectomy can be curative [35].

Since the surgical approach of the liver became more feasible and indicated, number of re-hepatectomies and adverse effects of chemotherapies are more common and have to be cautioning issue for surgeons. The liver parenchyma sparing denotes constant concerns for surgeons since the clearance of surgical margins are necessary and contrasting with the concerns on the volume of remnant liver necessary to avoid liver failure. Are et al. analyzed a total of 1019 patients who underwent hepatectomies for CRLM with surgery, a clear description of margin in a single institution, for the same team of surgeons and the same technique [36]. On univariate analysis, there were statistically significant differences in median survivals among all 3 groups: group (<1-10 mm) versus group (involved), 42 versus 30 months respectively, $p < 0.01$; and group (>10 mm) versus group (<1-10 mm), 55 versus 42 months respectively, $p < 0.01$. Margin width <1 cm retained statistical significance ($p < 0.01$) on multivariate analysis after adjusting for established risk factors. This study suggested that margin width of >1 cm is optimal and is an independent predictor of

survival after hepatic resection for colorectal metastasis. However, sub centimeter resections are also associated with favorable outcome and should not preclude patients from undergoing resection [36].

Additional Chemotherapy

It is therefore important to clarify definitions about regimens of chemotherapy that were mentioned in this review. Neoadjuvant therapy is the administration of preoperative systemic therapy for resectable hepatic metastases. In general, neoadjuvant therapy does not include any treatment after hepatic resection. The administration of chemotherapy, both before and after hepatic resection is referred to as perioperative. Adjuvant therapy is the administration of systemic therapy only after hepatic resection.

Adjuvant Chemotherapy

In the early 90's, Moertel et al. published the first adequate study contemplating adjuvant chemotherapy for CRC in stage II or III [8]. In this trial, patients underwent a curative resection without distant metastases (only regional nodes) received one year of 5-Fluorouracil (5-FU) and levamisole (antihelmintic agent with putative immunomodulating action) experienced a 33% of reduction in recurrence risk when compared with surgery alone. The Mayo Clinic group replaced levamisole for leucovorin (LV) and treated with 5-FU/LV for 6 months (Mayo Clinic Schedule or Roswell Park Schedule) with the same scope of patients [37]. They showed a similar benefit than 1 year of bolus 5-FU/levamisole. After these studies, adding Oxaliplatin as an adjuvant treatment was demonstrated in the MOSAIC trial [38]. In this study, patients with CRC in stage II or III had undergone resection with curative intent and received bolus plus continuous infusion of 5-FU/LV with the addition of oxaliplatin (FOLFOX 4). The updated results; 5-year DFS rates were 73.3% and 67.4% in the FOLFOX4 and 5-FU/LV groups, respectively (HR=0.80; 95% CI, 0.68 to 0.93; p=0.003). Six-year OS rates were 78.5% and 76.0% in the FOLFOX4 and LV5FU2 groups, respectively (hazard ratio [HR]=0.84; 95% CI, 0.71 to 1.00; p=0.046) [39].

The benefits of additional chemotherapy for CRC were the rationale for the use of systemic chemotherapy for CRLM. The role of adjuvant chemotherapy for CRLM was studied by Mitry et al. who made a pooled analysis of two phase III trials (Fédération Francophone de Cancérologie Digestive [FFCD] Trial AURC 9002 and the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia [ENG] trial) which evaluated patients undergone curative-intent hepatic resections of CRLM only (140 patients), compared to patients who the surgery was followed by 6 months of systemic adjuvant chemotherapy with a 5-FU and folinic acid monthly regimen (138 patients) [10]. The median Progression Free Survival (PFS) was 27.9 and 18.8 months (p=0.058) and median survival was 62.2 and 47.3 months, (p=0.095) for the chemotherapy and control groups, respectively. The authors concluded that the results of this analysis support the use of systemic chemotherapy, after potentially curative resection of CRLM. They also concluded that this study supports the alternative of resecting the disease immediately, thereby, avoiding the incidence of surgical complications in a chemotherapy-affected liver.

Following again the rationale of systemic therapy for CRC, de Gramont et al. published results from a phase III study that compared the effect of combining oxaliplatin to 5-FU/LV in 420 patients (210 in

each arm) previously untreated for CRLM [40]. Patients allocated to oxaliplatin plus 5FU/LV had significantly longer PFS (median, 9.0 versus 6.2 months; p=0.0003) and better response rates (50.7% versus 22.3%; p=0.0001) when compared with the controlled arm. The improvement in overall survival did not reach significance (median, 16.2 versus 14.7 months; p=0.12) [40].

Several retrospective series have shown a benefit for adjuvant treatment after liver resection of CRLM. Parks et al. in a multi-institutional study, reported on 792 patients, who had liver resections between 1991 and 1998 [41]. Among 792 patients who underwent liver resections, 518 of them were treated without chemotherapy and compared to the 274 patients treated with 5-FU based adjuvant chemotherapy. This study demonstrated increasing in overall survival rates even when clinical pathological features were adjusted by CRS [41]. The multivariate model demonstrated that positive margins (HR=1.59), bilateral liver tumors (HR=1.39), adjuvant and chemotherapy (HR=0.75) were also independent predictors of outcome. Ychou et al. related a randomized trial with 153 patients to bolus/ infusional 5-FU/LV or folinic acid, 5-FU and irinotecan (FOLFIRI) after liver resection [42]. During the course of follow-up over 42 months, the median DFS was not significant, 21.6 and 24.7 months for the 5-FU/LV and FOLFIRI groups, respectively (p=0.47).

The rationale for regional therapies in the liver after liver resection surged from evidences of the majority of recurrences after liver resection occur in the liver, and therefore, there has been interest in adjuvant Hepatic Arterial Infusion (HAI) in this setting. Liver metastases take their blood from the hepatic artery, whereas normal hepatic parenchyma derives most of its blood supply from the portal vein. In a study performed by Memorial Sloan-Kettering Cancer Center, Kemeny et al. reported patients were randomized to adjuvant HAI along with systemic 5-FU/LV versus systemic 5-FU/LV alone [43]. The endpoint, a 2-year survival was significantly increased for HAI along with systemic chemotherapy versus systemic alone, 86 versus 72%, (p=0.03). In an updated report, with a median follow-up of 10.3 years, the 10-year survival was 41.1 and 27.7% for HAI along with systemic and systemic groups, respectively. PFS was 31 versus 17 months (p=0.02) and hepatic PFS was not reached versus 32.5 months (p=0.001) for HAI along with systemic versus systemic groups respectively [44].

Neoadjuvant and Perioperative Chemotherapy

Nordlinger et al. in a phase III trial randomly assigned 364 patients with up to four resectable liver metastases to either six cycles of fluorouracil, leucovorin, and oxaliplatin (FOLFOX-4) before and six cycles after surgery or to surgery alone [11]. It is important to emphasize that this design's trial did not attempt to compare adjuvant to perioperative chemotherapy. The results demonstrated an increase in rate of PFS with perioperative chemotherapy at 3-years was 8.1% (p=0.041) in eligible patients. However, no significant differences in OS were detected in 3- or 5-years survival with median follow-up of 8.5 months [11,12]. Postoperative complications including biliary fistula (8% versus 4%), hepatic failure (7% versus 5%) and intra-abdominal infarction (7% versus 4%), were more common in the chemotherapy group (25 versus 16%, p=0.04) versus the surgery-alone group, respectively. The authors concluded that perioperative chemotherapy with FOLFOX-4 reduced the risk of progression in eligible and resected patients; their conclusion was that perioperative chemotherapy should be considered a standard of treatment in fact it has been considered the standard care by many practitioners world

widely. It has been established that oxaliplatin is more associated with sinusoidal and vascular injury than irinotecan which improves taxes of steatohepatitis associated with chemotherapy. Such specific chemotherapy-associated hepatic toxicity was not seen to this degree in the fluorouracil and leucovorin era.

Looking for neoadjuvant treatment, Gallagher et al. related an observational study that analyzed 111 patients who underwent a hepatectomy, preceded by neoadjuvant chemotherapy for resectable and synchronous CRLM from 1995 to 2003 [45]. The chemotherapy response was a complete response in 6 and a partial response in 41 patients (both 37%), stable disease in 52 patients (47%) and progressed disease in 18 patients (16%). There was no difference in survival between any of the response groups ($p=0.98$) and in patients who had undergone HAI or not ($p=0.12$) and the 5-year survival rate was 52%. The authors concluded that response rate to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases.

Chua et al. reported a systematic review about randomized and non-randomized trials of the clinical response and outcome of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases [46]. Twenty-three studies were reviewed: 1 phase III randomized control trial, 3 phase II studies, and 19 observational studies, comprising of 3,278 patients. Objective (complete/partial) radiological response was observed in 64% (range 44–100%) complete 4% (range 0–38%), partial 52% (range 10–90%) of patients after neoadjuvant chemotherapy. Pathologically, a median of 9% (range 2–24%) and 36% (range 20–60%) had complete and partial response, respectively. Among these patients, 41% (range 0–65%) had stable or progressive disease whilst on neoadjuvant chemotherapy. Median RFS was 21 (range 11–40) months. Median OS was 46 (range 20–67) months. European experts in hepatobiliary surgery and medical oncology has recommend the treatment of CRLM that the majority of patients could be treated upfront with systemic chemotherapy, irrespective of the resectability status of their metastases based on the results of the EORTC 40983 [11,12]. The potential benefit of preoperative chemotherapy could be to test the sensitivity and responsiveness of the tumor and thereby select the best regimen for postoperative treatment with adjuvant intent. However, several pitfalls have to be taken into consideration. The clinical decision for the best time for surgery and chemotherapy for these patients are still open, new studies comparing perioperative and neoadjuvant chemotherapy with adjuvant therapy for liver resection are required to clarify the risks and benefits ratios of preoperative chemotherapy administration.

Chemotoxicity

The increasing use of chemotherapy for colorectal liver metastases has raised awareness of the potential hepatotoxicities induced by systemic drugs and the effects of these drugs on outcome after hepatic resection. The increased use of preoperative chemotherapy for CRLM has led to a growing awareness of potential hepatotoxicity caused by such treatment. Clinical data have shown associations between specific chemotherapeutic drugs and histological changes in the liver. A key molecular event that might underlie chemotherapy-induced hepatotoxicity is the production of Reactive Oxygen Species (ROS), resulting in oxidative stress in hepatocytes [47]. Although the progression from steatosis to steatohepatitis is not completely understood, a two-phase mechanism of injury has been proposed. In the first phase, diseases such as insulin resistance, lead to an excess of fatty acids in hepatocytes which result in fatty-acid oxidation in

mitochondria and the production of ROS. Steatotic hepatocytes are more susceptible to a second phase of injury such as toxicity from chemotherapy, which leads to further generation of mitochondrial ROS and direct damage to mitochondria. With the oxidative capacity of the mitochondria impaired, extra mitochondrial fatty-acid oxidation systems are activated in microsomes and peroxisomes, leading to production of more ROS. The accumulation of ROS in hepatocytes causes lipid peroxidation of cell membranes, induction of pro-inflammatory cytokines, and expression of the Fas-ligand death receptor—causing fratricidal cell-killing. As well as cell death, lipid peroxidation of the cell membrane results in activation of stellate cells, subsequent collagen synthesis and fibrosis, and the generation of more ROS [47]. Causative association between fluorouracil and hepatic steatosis is unproven, and possible mechanisms by which fluorouracil might cause steatosis are poorly understood. Fluorouracil is associated with mitochondrial membrane collapse and a reduction in membrane potential that might impair oxidation of fatty acids and lead to subsequent accumulation of ROS within hepatocytes. Fluorouracil is also associated with the generation of ROS by microsomal cytochrome P450 enzymes.

Kobby et al. showed the results of a study comparing 325 patients with steatosis who underwent a surgery versus 160 patients with normal liver parenchyma in a group control. There were 223 patients with mild and 102 with marked steatosis [48]. Those with steatosis were more likely to be men (59% marked vs. 55% mild vs. 43% control; $p=0.01$) with a higher body mass index (29.7 ± 5.5 marked versus 28.2 ± 5.5 mild versus 26.0 ± 5.4 control; $p<0.01$), and treated preoperatively with chemotherapy (66% marked versus 55% mild versus 38% control; $p<0.01$). Total (62%, 48%, and 35%; $p<0.01$) and infective (43%, 24%, and 14%; $p<0.01$) complications correlated with the degree of steatosis. There were no differences observed in complications requiring major medical intervention, hospitalization or admission to the intensive care unit between groups. The authors concluded that the marked steatosis is an independent predictor of complications following hepatic resection but does not have a significant impact on 60-day mortality. Steatosis alone should not preclude aggressive hepatic resection for neoplasms when indicated; however, patients with marked steatosis undergoing large resections should still be approached with caution [48]. Vauthey et al. studied chemotherapy-associated liver injury and irinotecan which associated with the development of steatohepatitis in four of 33 (12%) of patients with BMI less than 25 kg/m^2 and 15 of 61 (25%) with BMI of 25 kg/m^2 or more [49]. The molecular basis for the association between irinotecan and steatohepatitis is not well-defined. It was found that simple steatosis was not associated with increased postoperative morbidity or mortality. However, many patients with steatosis have other comorbid conditions, such as obesity and diabetes that can increase the risk of complications. By contrast with simple steatosis, which does not have a substantial effect on postoperative outcome, steatohepatitis is usually a contraindication to major liver resection. In the same study, it was reported that a 90-day mortality of 15% in patients with steatohepatitis compared with 2% in patients without steatohepatitis ($p=0.001$). The authors also proposed the optimum duration of preoperative chemotherapy to maximize therapeutic benefit while avoiding hepatotoxicity which is likely to be 4 months at most. They analyzed patients who received short-course oxaliplatin for 3–4 months, which was not associated with increased morbidity or mortality after hepatic resection [49].

Discussion

Resection is the standard of care for local treatment CRLM initially resectable or converted to a potentially curable disease after chemotherapy. Most of practitioners adopted additional chemotherapy as standard of care; however the optimal timing for chemotherapy for CRLM remains controversial. The performance status, disease's aggressiveness, tumor burden and location defining potential resectable lesions are the most important parameters to decide among possible treatments. Resection are just valid if complete removal of all CRLM is realistically possible, since partial liver resection or debulking has not been shown to be beneficial [16,50].

Unresectable Liver Disease

For this group of patients, the preoperative chemotherapy has to be considered with the intention to convert these lesions to potentially curable disease after chemotherapy [51]. Adam et al. reported a study with 1439 patients initially unresectable CRLM, 1104 patients were treated with chemotherapy and 335 patients underwent surgery [52]. Among the 1104 patients receiving chemotherapy, 138 patients (12.5%) classified as "good responders" underwent secondary hepatectomies. The 5-year survival rate for these 138 patients was 33%. Resection of primary CRC prior to initiate the chemotherapy is rarely necessary, and should only be done in patients with severe symptoms (important bleeding or intestinal obstruction, abscess, etc.) related to primary cancer. Advantages to neoadjuvant chemotherapy include the possibility of downsizing both the primary tumor and CRLM, and very low rates of complications related to the unresected primary cancer [53].

The National Comprehensive Cancer Network (NCCN) recommends that a surgical re-evaluation should be planned 2 months after initiation of preoperative chemotherapy for those patients [51]. Those who continue to receive preoperative chemotherapy undergo surgical re-evaluation approximately every 2 months thereafter. To limit development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable. Patients not responding or progressing with the disease during preoperative chemotherapy, should receive chemotherapy for advanced or metastatic disease with treatment selection based in the clinical performance status of patients, if they are appropriate candidates for intensive therapy. The NCCN also discourages the use of conformational external radiation therapy unless the patient is symptomatic or it is used in a clinical trial [51].

Resectable Liver Disease

The best timing for additional chemotherapy in a patient with resectable CRLM represents a difficult decision for clinical and surgical oncologists since the optimal sequence of treatment has not been defined. Whether to administer chemotherapy in a perioperative or adjuvant fashion has not been specifically addressed by randomized trials. A series of 411 patients from Memorial Sloan-Kettering Cancer Center with initially resectable CRLM attempted to address this question in a retrospective view of ten years practice [54]. Araujo et al. compared 175 patients who underwent perioperative regimen to 236 patients who underwent adjuvant regimen. The groups were different with perioperative group presenting patients with smaller tumors, shorter disease-free intervals, more metastases and they more frequently bilateral disease. No differences in OS were detected. RFS rates were statistically better for those who received adjuvant

chemotherapy than for patients in the perioperative regimen (5-years RFS of 38% and 31%, respectively, $p=0.036$). However, once the RFS was adjusted for CRS (high and low risk of recurrence by Fong CRS), the differences between the groups were no longer significant [16,54].

Perioperative chemotherapy has been administered with the main intention to downsize CRLM in order to convert unsusceptible lesions in resectable. Another potential advantage this approach may include, is the early treatment of micrometastatic disease and determination of responsiveness to chemotherapy, which can be a prognostic marker avoiding local therapy treatment instead of systemic therapy for patients with early disease progression [51]. This rationale is clear for patients with initially unsusceptible CRLM, since they are excluded of initial surgical treatment that is the standard of care for local treatment for CRLM [16,17]. However, in patients suitable for resections, the potential disadvantages for perioperative chemotherapy should be considered: chemotherapy-induced liver injury increasing morbidity of procedure, and missing the "window of opportunity" for resection through the possibility of either disease progression or achievement of complete clinical and radiologic response (without pathological confirmation) becoming difficult to identify areas for resection [46,48]. The EORTC trial 4093 described a progression rate of 7% during preoperative chemotherapy in the perioperative regimen [11].

Synchronous Metastases

Short disease free-interval is well established as independent prognostic factor and when simultaneous presentation of colorectal and liver metastasis plays a different role in the decision of surgery [15,16]. In a retrospective, multi-institutional analysis with 610 patients who underwent simultaneous ($n=135$) or staged ($n=475$) resections of CRC and Synchronous CRLM, Reddy et al. compared postoperative outcomes [50]. Simultaneous patients had fewer (median 1 versus 2) and smaller (median 2.5 versus 3.5 cm) metastases and less often underwent major (\geq three segments) hepatectomy (26.7% versus 61.3%, $p<0.05$). Mortality (1.0% versus 0.5%) and severe morbidity (14.1% versus 12.5%) were similar after simultaneous colorectal resection and minor hepatectomy compared with isolated minor hepatectomy. Otherwise, for major hepatectomy, simultaneous colorectal resection increased mortality (8.3% versus 1.4%, $p<0.05$) and severe morbidity (36.1% versus 15.1%, $p<0.05$). Combined severe morbidity after staged resections was compared lower to simultaneous resections (36.1% versus 17.6%, $p=0.05$) for major hepatectomy but similar for minor hepatectomy (14.1% versus 10.5%, $p>0.05$). Major hepatectomy independently predicted severe morbidity after simultaneous resections (HR=3.4, $p=0.008$). The authors conclude that simultaneous colorectal and minor hepatic resections are safe and should be performed for most patients with Synchronous CRLM [50]. However, some criticism for this study should be considered since there was a retrospective analysis with 21 institutions, over a 21 year period with different kinds of chemotherapy and surgical techniques and the selection criteria for simultaneous resection were not clear among those institutions.

The same argument used to delay the resection of primary CRC prior to initiation of chemotherapy in unsusceptible CRLM could be considered to resectable CRLM. Therefore, resection of primary CRC is rarely necessary before of CRLM treatment and could only be done in patients with severe symptoms related to primary cancer. Furthermore, neoadjuvant chemotherapy includes the possibility of downsizing both the primary tumor and CRLM, and very low rates of complications related to the unsuspected primary cancer [53]. The

rationale of this “reverse strategy” is to provide treatment of the metastatic disease of avoiding delays by local therapy for the primary tumor (surgery, and in the case of rectal cancer, radiotherapy or radiochemotherapy) or by complications of surgical treatment of the primary tumor [55]. Brouquet et al. related a series of 156 patients with synchronous CRLM initially resectable and intact primary treated in different surgical strategies: 142 patients who had resection of all disease, 72 patients underwent a classic (primary before liver), 43 combined (combined resection of primary and liver) and 27 reverse (liver before primary). Median numbers of CRLM per patient were 1 in the combined group, 3 in the classic, and 4 in the reverse strategy group ($p=0.01$ classic versus reverse; $p<0.001$ reverse versus combined). Postoperative mortality rates; postoperative cumulative morbidity rates; 3-year and 5-year overall survival rates in the combined, classic, and reverse strategies did not have relevant statistical differences. On multivariate analysis, liver tumor size ≥ 3 cm (HR=2.72, 95% CI 1.52 to 4.88) and cumulative postoperative morbidity (HR=1.8, 95% CI 1.03 to 3.19) were independently associated with overall survival after surgery. The authors concluded that the reverse strategy can be considered as an alternative option in patients with advanced CRLM and an asymptomatic primary [55].

Conclusion

Many considerations should be taken based on randomized and non-randomized trials for the management of CRLM. The pros for use of adjuvant chemotherapy for CRLM are the earlier surgical treatment (the standard of care) and non-damaged liver parenchyma against the cons of undetected progressing disease and larger hepatectomies. Looking for neoadjuvant or perioperative chemotherapy, they present pros of downsizing of lesions and evaluation of chemotherapy responsiveness before hepatectomy. The cons of preoperative chemotherapy are the risk of delaying surgical treatment in bad chemotherapy responders hindering curative-intent treatment by local progression or distant metastases; systemic and hepatic toxicity could increase the risk of intra-operative and postoperative complications. The patient selection for a “good responder” in each modality should be considered as the principal pattern of management of patients with CRLM; the main point is to deduce who has high risk to progress disease with extra-hepatic metastases which is markedly a worse prognosis. The pros for a simultaneous approach would be early treatment of CRLM with a non-affected remnant liver. Otherwise, the cons would be the risk of progressive disease just after surgery appearing an aggressive disease with the onus of hepatectomy; higher hepatectomies that could be reduced if the patient answered to chemotherapy; the risk of infection could be higher and justified by the bowel manipulation and longer time of surgical procedure. The pros for stage treatment are: conversion of borderline or unsuspected CRLM in resectable and allowing liver parenchyma sparing; the patient’s selection based on the responsiveness of chemotherapy revealing options for adjuvant therapy or avoiding those “bad responders” who undergo supposed curative hepatectomies. The cons of stage treatment are: delays on hepatic resection with the risk to lose the opportunity of curative treatment if the disease progresses the risk of chemotoxicity of liver with increase of morbidity or the loss of clinical status to undergo surgery; and radiologic response and not permit to identify the correct site in the liver to be unsuspected. Although, the synchronous CRLM per se is already a maker of aggressive disease, this group also have “good responder” to the simultaneous treatment and they are patients with: CEA at diagnosis or prior to laparotomy ≤ 200 ng/mL, ≤ 4 tumors, unilobar metastases,

node-negative primary tumor, largest metastasis ≤ 5 cm [56]. This way, they are candidates to minor hepatectomies following easier recovery with lower morbidity and permitting adjuvant chemotherapy. Otherwise, patients with high risk markers should be preferred to stage resection to use the advantage of downsize and selected chemo responsiveness, avoiding putative hepatectomies with cure intention.

In summary, progresses in surgical field and systemic treatment for CRLM have been changing the oncologic approach for treatment of CRLM. The unsuspected liver disease could be overtaken in a relevant group of patients since advantage of preoperative chemotherapy and surgical techniques would increase and preserve remnant liver parenchyma. Otherwise, the chemotoxicity should always be considered. If preoperative chemotherapy is selected, the number of courses should be minimized and surgical reevaluation is advised to evaluate the chemo response and avoid unnecessary chemotoxicity. It is undeniable that there is a lack of evidence in the literature covering comparisons between perioperative to adjuvant chemotherapy for patients with CRLM. Thus, the use of extrapolated results obtained in retrospective series and RCT in patients with stage IV whom underwent regimens of chemotherapies compared to surgery alone have been taken to provide treatment for CRLM patients. It seems that chemotherapy should always be offered as additional treatment to curative-intention liver resections, increasing RFS, but not affecting OS. The optimal timing for each chemotherapy regimen has not been answered for any RCT trial yet. Retrospective series are biased on different patient selection for different chemo modalities. The best candidate for each regimen of chemotherapy could not yet be defined, but clearly patients with more aggressive disease have being preferred to preoperative chemo regimens. Preoperative chemo has been done to test the chemo responsiveness. These patient selection criteria have not been answered yet but the rational additional chemotherapy, regardless the timing of administration, has been assumed as stand of care for patients who underwent curative-intent resection.

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