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COLORECTAL LIVER METASTASES (S WEBER, SECTION EDITOR)

Treatment of Unresectable Liver-Only Disease: Systemic Therapy versus Locoregional Therapy

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Abstract Most patients with colorectal liver metastases present with unresectable/disseminated disease and are treated with palliative therapies. Patients with unresectable liver only disease represent a large subset that similarly has a poor prognosis. Numerous reports pertaining to local and systemic therapies have been published, there are however few methodologically rigorous studies to define the best approach in these patients. Most information comes from retrospective reports at high volume centers, which does not necessarily represent the current treatment for the majority of patients. The aim of this review is to analyze the current systemic and local treatments utilized in these patients with the aim of defining the ideal approach for them.

Keywords Liver metastases · Systemic therapy · Locoregional therapy · Unresectable liver-only disease · Intra-arterial chemotherapy · Directed radiotherapy · Colorectal cancer · Treatment · Survival

Introduction

Colorectal cancer is the fourth most common cancer and the second cause of cancer death in the USA. Its mortality has decreased dramatically; nonetheless, an important proportion of patients present with metastatic disease [1].

The liver is the most frequent solid organ involved with metastases [2]. Approximately 15–25 % of patients diagnosed with a colorectal cancer present with liver metastasis (CLM) at the moment of diagnosis and about 50 % develop CLM during their follow-up. Moreover, patients may present with a wide spectrum of clinical scenarios that impact their treatment and survival [3]. To facilitate comparisons, patients are usually divided in a group with liver-only disease (LOD) and another with extrahepatic disease (EHD) to better define the therapy and prognosis [4].

Complete resection/ablation is the treatment of choice for patients with resectable CLM because it is the only therapy that may lead to long-term survival and cure [5]. Survival is significantly worse in patients treated only with chemotherapy [6]. Despite all these considerations, selecting patients for surgery may be challenging and depends on multiple factors such as extent of disease (intra and extra hepatic), surgical expertise, extent of future liver remnant, overall patient fitness and performance status, comorbid medical conditions, and tumor biology [7].

Patients with isolated liver disease may be approached differently, depending on the extent of disease. While there is consensus that those patients with limited disease (i.e., one liver metastasis) should be treated with resection up front [2], it has been difficult to define the best treatment for patients who present with extensive but resectable disease. Some centers define this group as *"potentially"* unresectable, based more on the biology of disease than on real anatomical factors of resectability, and suggest that neoadjuvant chemotherapy could help to select those patients that may benefit from surgery [8]. In contrast, patients with *truly* unresectable disease (related to extension of disease, anatomical factors or liver remnant) should

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be treated initially with systemic and/or regional therapies, with the main aim of downsizing the tumors to achieve a chance for complete resection, which is the treatment that may improve survival in this subgroup of patients [9•].

This review is focused on patients with CLM who present with unresectable isolated liver disease and evaluates local and systemic treatments. For the purpose of this article, the role of (truly) neoadjuvant chemotherapy only will be discussed to better understand the biology and prognosis of patients with extensive resectable disease, which is also important in helping to define the prognosis of patients with unresectable liver metastases.

Definition of Unresectable Disease Confined to the Liver

Unresectable disease is defined by anatomic considerations and/or functional factors. Liver resection must include the preservation of two contiguous segments of liver, the ability to preserve adequate vascular inflow, outflow, biliary drainage, and future liver remnant volume and function. A margin-negative resection is also expected.

Some high-volume centers have shown that ultra-selected candidates may undergo complete resection with acceptable morbidity using non-conventional surgical techniques such as ex vivo, ante-situm, or ALPPS resections [10–15]. The amount of liver remnant is another factor that must be considered when defining who is a surgical candidate [16]. Moreover, the quality of the liver, the number of cycles of chemotherapy received, and the comorbidities are all important factors that must be considered when defining what an adequate liver remnant volume is. There is consensus that it is necessary to have 25–30 % of the liver preserved as the future liver remnant volume when liver is normal and as high as 40 % in patients who have injured livers: those who have received extensive preoperative chemotherapy, have steatosis, or have diabetes mellitus [7]. Patients with diabetes have a decreased rate of regeneration and therefore should be evaluated carefully. Thus, every patient should have a formal quantification of the future liver remnant before surgical exploration, and portal vein embolization (PVE) should be considered in borderline cases [17–20]. A two-stage hepatectomy is another option in patients with high risk of liver failure. In this procedure, a compensatory liver regeneration after a first non-curative hepatectomy allows a second, potentially curative surgery. It has been observed that chemotherapy after PVE does not decrease the hypertrophy of the remnant liver nor increase the postoperative complication, but may be useful to decrease the risk of developing new tumors during the month that it is necessary to wait before resection [21, 22•].

Finally, it is important to note that patients with limited CLM and potential good tumor biology may have an adverse prognosis because their disease is unresectable because of anatomical or functional problems. Since the concept of unresectability may be variable among centers, every patient must be evaluated within the context of a multidisciplinary team, which should include a surgeon with expertise and experience in liver surgery, before deciding that the disease is unresectable because in some patients a two-stage hepatectomy could be performed [9•, 23, 24].

Natural History of Patients with Extensive/Unresectable LOD

Approximately 80 % of patients with CLM will present with unresectable disease [5, 6]. In the past, the majority were treated with palliative chemotherapy, and the survival was less than 1 year. Contemporary series that employ the combination of new drugs developed over the last 20 years have shown marked improvements in both tumor response and survival [2]. Nevertheless, in patients treated exclusively with chemotherapy, the median survival is less than 2 years, which is significantly lower than in patients treated with complete resection, demonstrating that surgical resection provides the only chance for cure.

Several retrospective studies have analyzed the natural history of patients with unresectable LOD. Bismuth et al. [25] evaluated 434 patients with CLM. The majority ($n = 330$, 76 %) were considered unresectable because the authors considered that it was not possible to perform a complete resection and received systemic chemotherapy [5-fluorouracil (5-FU), folinic acid, and oxaliplatin (Ox)]. Only 53 (16 %) patients had an adequate downsizing to undergo resection. The majority required a major hepatectomy ($n = 37$, 70 %) in one-stage ($n = 46$), and PVE was uncommon ($n = 5$, 9 %). Importantly, after a median follow-up of 42 months, 34 (66 %) patients had recurrence in the liver, and 25 (47 %) patients had extrahepatic recurrences. At last follow-up, 23 patients had died from disease and 19 were free of disease, but 14 of these 19 patients required repeat liver resection after recurrence to become NED. Five-year estimated overall survival (OS) was 40 %. This series demonstrated that only a small percentage (16 %) of patients with unresectable disease will ever achieve surgical resection, and in this subset of patients, multiple resections were needed to improve survival. Adam et al. [5] updated the experience of the same group and evaluated 1,439 patients treated over a period of 11 years (Fig. 1). As in the previous experience, the majority ($n = 1{,}104$, 77 %) presented with unresectable disease, based on the same author's definition [25] and

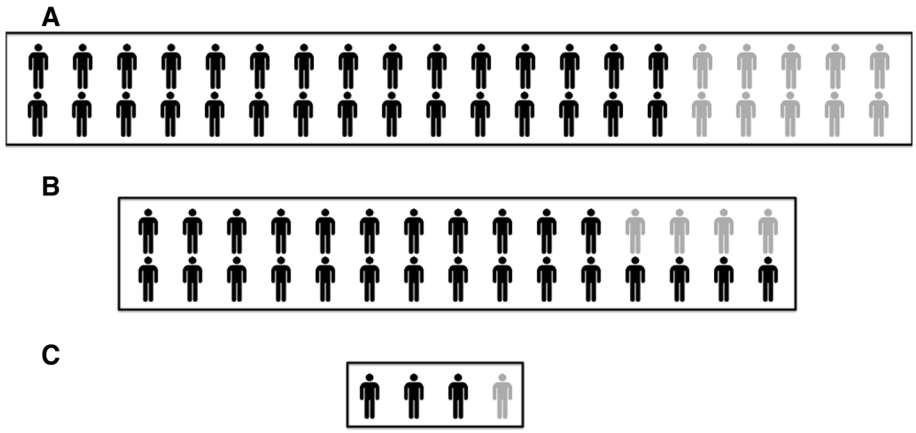

Fig. 1 Schematic representation of patients with CLM at the moment of diagnosis. **a** About 75 % of patients will have unresectable disease. **b** About 15 % will convert from unresectable to resectable disease after chemotherapy; **c** only 25 % of those patients who converted to resection after chemotherapy will finally be free of disease at the moment of last follow-up. Thus, 1 of 30 (3 %) patients presenting with unresectable disease will be free of disease at the moment of last follow-up

received systemic chemotherapy [5-FU plus leucovorin combined with Ox (70 %), irinotecan (Iri) (7 %), or both (4 %)]. After a median number of ten cycles, 138 (12.5 %) patients responded adequately and underwent liver resection (93 % with curative intent). Despite this, most patients responded to first line chemotherapy, but 14 % required a second and 9 % a third line. This series also included 52 (38 %) patients who presented with EHD, mainly involving the lungs, and resection was performed in 41 of them. Fifteen patients required a two-stage hepatectomy, 15 at least one ablation, and 9 % underwent PVE. After a mean follow-up of 48 months, 111 out of 138 (80 %) patients recurred, intrahepatic ($n = 40$, 29 %), extrahepatic ($n = 12$, 9 %), or both ($n = 59$, 43 %). A new hepatectomy after liver recurrence was performed in 55 patients, and a new extrahepatic recurrence was extirpated in 28 patients. At the moment of analysis, 99 patients had died and 25 were free of disease. Five-year DFS and OS were 22 and 33 %. Four factors (rectal primary, ≥ 3 metastases, preoperative CA19-9 > 100 UI/l, and preoperative tumor size >10 cm) predicted OS, decreasing significantly from 59 % (without any factor) to 0 % when 4 factors were present. Recently, Adam et al. [6] focused their analysis on 184 consecutive patients who presented with unresectable disease, but underwent complete resection after tumor downsizing. As previously described, most patients had advanced disease (bilobar involvement in 76 %) and needed a median of ten cycles to convert. Despite this, most patients had a follow-up of 5 years or more, 112 (76 %) died from disease after this period, and only 24 (16 %) were considered cured (most after the first hepatectomy).

In another retrospective study, Komprat et al. [26] evaluated 98 patients with four or more CLMs who underwent complete resection at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1998 and 2002 (17 % of resections of that period). This subgroup clearly had an aggressive disease since the median number of tumors and size was 5 and 4.3 cm, respectively, and the CLM was diagnosed within 12 months of initial surgery in most patients. The majority (55 %) received neoadjuvant chemotherapy (median = 7 months), and progression during this treatment was documented in 28 %. The majority of patients underwent an aggressive surgical treatment [extended (45 %) or hemi (32 %) hepatectomy, and additional resection/ablation of another hepatic lesion (46 %)]. Resection of EHD was performed in 18 patients, but for local extension of the liver metastases in most of them. Ninety-two percent received adjuvant chemotherapy. Importantly, most patients (57 %) recurred during the first year, and the median disease-free survival (DFS) from resection was 12 months. After a median follow-up of 33 months, 51 % of patients had died of disease, 30 % were alive with disease, and 19 % had no evidence of disease. Five-year OS was 33 %, and patients who progressed during chemotherapy had the worst survival. This series included seven 5-year survivors, but all had recurred. This study outlines the natural history of those patients who are not necessarily unresectable at the moment of diagnosis, but present with advanced disease.

In another European study, Ardito et al. [27•] evaluated the chance of cure in patients who presented with unresectable LOD. This series evaluated 61 patients without EHD and exclusively treated with liver resection. Most patients received irinotecan-based chemotherapy, and resectability was achieved after a mean number of 11 cycles. Thirty-one patients required a major hepatectomy, which was associated with a PVE in seven, and nine patients were candidates for a two-stage hepatectomy (completed in 5). Despite extensive treatment, only 45 (74 %) patients underwent an R0 resection. Forty-four

Table 1 Selected series of patients included in retrospective studies

Study	No patients	Unresectable or aggressive biology at presentation	Adequate response after chemotherapy	Recurrence	5-year overall survival (%)
Bismuth et al.	434	330 (76 %)	53/330 (16 %)	Hepatic = 34 (66 %) Extrahepatic = 25 (47 %)	40
Adam et al.	1,439	1104 (77 %)	138/1104 (12.5 %)	111 (80 %)	33
Komprat et al.	584	98 (17 %)	19 (35 %)*	81 (83 %)	33
Ardito et al.		61	–	44 (79 %)	43

*Only 54 (55 %) patients received chemotherapy before surgery

(79 %) patients recurred, and a new resection was performed in 15. After a median follow-up of 39 months, 5-year RFS and OS were 23 and 43 %, respectively. OS was highly correlated with complete resection (68 months in R0 resection). Despite 30 patients completing 5 years of follow-up, only 11 were alive at the moment of analysis. More recently, the University of Toronto evaluated 24 patients who were considered initially unresectable. The majority had advanced disease [bilobar disease ($n = 23$), median number of tumors = 7, median size of tumor = 7 cm]. All patients received oxaliplatin/irinotecan-based chemotherapy. Twenty out of 24 (83 %) underwent an R0 resection, but most patients ($n = 18$) recurred within 9 months. Three-year DFS and OS were 19 and 55 %.

These retrospective studies demonstrate the natural history of patients who present with unresectable LOD and allow us to draw some conclusions about how best to treat them (Table 1). First, all patients should undergo comprehensive medical and surgical treatment to achieve complete resection at centers with expertise in complex hepatic surgery. Second, despite our best efforts, only 17 % of patients will achieve resection, and the majority of patients will recur after resection, but the survival is significantly better than historical controls of patients treated with chemotherapy alone. Thus, the effort should be applied in every patient, and a prospective randomized trial is not needed and unethical at this point. Third, patients who progress during chemotherapy have the worst prognosis. This situation defines a group of patients who have tumors with aggressive biology and a high chance of progression despite our best surgical efforts.

Prospective Trials Including Systemic Treatment in Patients with Unresectable LOD

Systemic chemotherapy is the most common treatment utilized in the majority of patients who present with unresectable LOD. Different combinations of drugs have been tested in prospective phase II trials, which have been designed to determine the rate of response. The most frequently used drugs are: 5-FU/leucovorin, oxaliplatin, irinitecan, bevacizumab, and cetuximab.

Alberts et al. [28], as part of the North Central Cancer Treatment Group, evaluated the role of FOLFOX in patients with unresectable LOD. Forty-four patients were enrolled from 13 institutions, and 42 were treated. Eleven (26 %) patients had received previous treatment, and the main reason for unresectability was the number of lesions in 19 (45 %) patients, which was assessed by a surgeon with experience in liver surgery, before starting the treatment. Patients received chemotherapy biweekly until best response or progression/toxicity. Resectability was evaluated at 6 and 12 weeks after starting chemotherapy, and at least two cycles of FOLFOX were planned after resection. After a median number of ten cycles, a reduction of tumor size was observed in 25 (60 %) patients, and 17 (40 %) underwent surgical exploration. Complete resection was obtained in 14 (33 %) patients, partial resection in 1, and 2 were not resected. Ten (67 %) patients received adjuvant chemotherapy. After a median follow-up of 22 months, recurrence was observed in 11 out of 15 (73 %) patients treated with resection. The majority were located in the liver. Median time to recurrence was 19 months. At the moment of analysis, 31 (74 %) patients had died. Median OS was 26 months, and median OS for patients undergoing resection was not determined because 67 % were alive at 3 years.

Ychou et al. [29] in another phase II trial evaluated the role of FOLFIRINOX in patients with unresectable LOD (defined by two liver surgeons and two radiologists) with the aim of determining the rate of R0 resection. Every patient was treated every 2 weeks until completing 12 cycles or having progression/toxicity. Thirty-four patients were enrolled and evaluated, but 11 patients had minor protocol violations that included the inclusion of one patient with carcinomatosis, another with resectable disease, five with lung metastases, and two who underwent liver resection before entering in the study. Partial and complete response was observed in 23 and 1 patients, respectively. By contrast, only three patients had progression of disease. The median time between treatment and surgery was 4 months, and hepatic resection and/or

ablation was performed in 28 (82.4 %) patients (liver resection alone = 15, liver resection plus ablation = 10, and ablation alone = 3). Complete resection was performed in 9 out of 34 (26.5 %) patients. However, after a median follow-up of 31 months, 8 out of 9 (89 %) patients recurred, mainly in the liver ($n = 7$). Median RFS and OS were 13.9 and 36 months, and 2-year OS was 83 %. Importantly, every patient had at least one adverse event related to the treatment, and at least one grade 3 or 4 toxicity was observed in 26 (76.5 %) patients. The most frequent complications were neutropenia and diarrhea.

Massi et al. [30] evaluated the long-term outcome of 196 patients enrolled in three trials who presented with unresectable disease and were treated with FOLFOXIRI followed by radical surgery. The therapy was given for 12 cycles or until evidence of progression/toxicity. This study included 73 (37 %) patients with liver metastases. This is important because it evaluates the effectiveness of this treatment for metastatic colorectal cancer. Chemotherapy was effective in 138 of 196 (70 %) patients, but only 37 out of 196 (19 %) patients underwent a surgery with curative intent. Adequate response that promoted complete resection was more common in patients with LOD (25 of 73 patients with liver metastases, 34 %) and better than at other sites of metastatic disease (25 of 37 patients completely resected, 68 %). The 37 patients who underwent surgical exploration received a median number of 11 cycles, and the median time of preoperative chemotherapy was 5.5 months. Liver resection included a major hepatectomy in 19 (52 %) patients, but 8 were also treated with radiofrequency ablation. Complete pathological response was observed in four patients with LOD. After a median follow-up of 67 months, 31 out of 37 (84 %) patients recurred. PFS was 18 months from study entry, but if we consider that the median time between chemotherapy and surgery was 5.5 months, patients recurred at a median time of 12 months after surgery. Importantly, the six patients who have not recurred had LOD, suggesting that in this group of high-risk patients, those with LOD have a better prognosis. A second resection was performed in 11 out of 31 patients who presented with recurrence. Median and 5-year OS was 40 months and 42 %. However, the survival was better in patients with LOD (median = 61 months, 5-years = 43 %). The best survival between the 196 patients evaluated was observed in those patients with LOD who underwent R0 resection and had complete pathologic response (median = 64 months, 5-years = 75 %).

In another phase II trial, Skof et al. [31] compared the effectiveness of XELIRI (capecitabine plus irinotecan) vs. FOLFIRI (5-FU/LV plus irinotecan) in patients with unresectable LOD, with the aim of determining the rate of response and resection. Forty-one patients were treated with XELIRI and 46 with FOLFIRI, but the study was closed prematurely (43 % of initially planed accrual) because bevacizumab became a part of the standard of care for the authors. Median duration of treatment was 5 and 5.1 months, respectively, and both treatments had a comparable rate of toxicity. Both groups had a similar response rate (XELIRI = 49 % vs. FOLFIRI = 48 %), probability of complete resection (XELIRI = 29 % vs. FOLFIRI = 44 %, $p = 0.16$), and rate of R0 resection (24 %). Complete radiologic response was observed in five (7 %) patients treated with XELIRI and one (2 %) with FOLFIRI, but they did not undergo resection. At the moment of analysis, 37 % of patients treated with XELIRI and 26 % with FOLFIRI did not have recurrence. Both treatments had a similar median PFS (XELIRI = 10.3 months vs. FOLFIRI = 9.3 months, $p = 0.78$) and OS (XELIRI = 30.7 months vs. FOLFIRI = 16.6 months, $p = 0.16$). However, it should be noted that there was a trend toward better survival in the group treated with XELIRI. Since this study was not powered to answer this question, a larger phase III trial with an adequate statistical power is needed.

Another phase II trial conducted by Zhao et al. [32] focused only on the role of XELIRI in patients with unresectable LOD. Forty-eight patients were enrolled, and 47 were assessed for response. Twenty-nine patients had some grade of response, and 18 had a partial response. Surgical exploration was performed in 23 patients (49 %) [R0 resection = 20, incomplete resection = 2 (based on the postoperative CT), no resection = 1]. After a median follow-up of 24 months, 13 out of 22 (59 %) resected patients had recurred, mainly in the liver remnant. The median time to progression for patients treated with complete resection was 23 months, while the median and 3-year OS was 27.5 months and 29 %.

Wong et al. [33] evaluated the role of a combination of capecitabine, oxaliplatin, and bevacizumab in 45 patients who were not selected for upfront resection. Despite the fact that this trial included patients who were not necessarily unresectable at the time of presentation, it is important to know the relevance of this treatment in patients with a high risk of recurrence to better understand the biology of this disease. Ten of 15 (67 %) initially resectable patients (with their primary in situ) underwent resection (R0 = 6 and R1 = 4). On the other hand, 12 of 30 (40 %) initially unresectable patients converted to resectable, but 8 underwent resection (2 other patients had complete response and 2 others were not surgical candidates). Despite this positive result, only 3 out of 8 underwent an R0 resection, and in total 18 out of 45 (40 %) underwent a liver resection (R0 = 9, 20 %). The authors report 1-year PFS and OS of 50 and 86 %, but it should be considered that the median follow-up was only 12.5 months, which is a small interval to make a conclusion about survival. Thirty-eight grade 3 complications

Table 2 Selected series of patients with unresectable liver disease treated in a prospective trial

Study	Number of patients treated	Treatment	Response	R0 resection	Recurrence	Median OS (months)
Alberts et al.	42	FOLFOX	25 (60 %)	14	11 (73 %)	26
Ychou et al.	34	FOLFOXIRI	24 (71 %)	9	8/9 (89 %)	36
Skof et al.	41	FOLFIRI	20 (49 %)	11	_	30.7
	46	XELIRI	22 (48 %)	10		16.6
Zhao et al.	47	XELIRI	29 (62 %)	20 R1 = 2	13/22 (59 %)	27.5
Takahashi et al.	36	FOLFOX	18 (50 %)	13	_	_
Ji et al.	73	FOLFOX+cetuximab	53 (73 %)	20	_	_

OS overall survival

related to cabecitabine/oxaliplatin and five grade 3 complications and two grade 4 complications associated with bevacizumab were observed.

More recently, Takahashi et al. [34••] evaluated the role of modified FOLFOX in patients with unresectable LOD in a multicenter study (38 centers). The main objective was to determine the rate of curative surgery. Thirty-six patients without ED and without a previous history of chemotherapy with oxaliplatin/irinotecan were included. Most patients presented with advanced disease [more than 5 tumors = 28 (78 %), 20 (56 %) patients had tumors larger than 5 cm] and received six to eight cycles of FOLFOX. An additional six cycles were recommended after surgery. Thirty-one (86 %) patients completed the treatment with a median of six cycles [partial response = 18 (50 %), stable disease = 12, progression = 4]. Fourteen out of 36 (39 %) patients underwent surgical exploration, and 13 had an R0 resection. Survival was not mentioned in this study.

Finally, Ji et al. [35••] evaluated 73 patients with unresectable LOD and K-RAS wild type, enrolled at eight Korean centers. Each patient received FOLFOX plus cetuximab every 2 weeks for a maximum of 12 cycles, and 46 completed the treatment. A partial response was observed in 53 (73 %) patients, and 36 (49 %) underwent surgical exploration [R0 resection = 20 out of 73 (27 %), including radiofrequency ablation in 6, R1 = 6, and R2 = 10]. Median time to progression in all patients and in those treated with R0 resection was 9.8 and 14 months, respectively. At the time of analysis, 56 (77 %) patients had progressed, and 23 (32 %) had died of disease. The most common hematologic complication was thrombocytopenia (49 %), while the most common non-hematologic complication was skin rash (28 %). Table 2 shows selected series of patients included in prospective trials.

Regional Treatments

The rationale for using regional therapies in patients with unresectable LOD is that the treatments may be focused in the liver, increasing the local activity, and decreasing the systemic toxicity. In this section of this review, we discuss the most common regional treatment currently used; hepatic-arterial infusion pump (HAIP) chemotherapy and directed radiotherapy are discussed.

HAIP Chemotherapy

In patients with unresectable LOD, HAIP chemotherapy has the advantage that higher doses of chemotherapy can be used without increasing the systemic toxicity [36]. Different modalities have been used to deliver the drugs, but implantable pumps are the most common, since they are associated with fewer complications when compared with other forms of delivery [37]. Before inserting a pump, it is important to rule out the presence of EHD and to define the arterial anatomy. The main proponent of this technique in the US has been MSKCC, which is the center with the greatest experience with this treatment [38–40]. After exploring the abdominal cavity to exclude metastatic disease, a cholecystectomy and a complete ligation of all collateral arteries to the duodenum, bile duct, pancreas, and stomach should be performed. The gastroduodenal artery (GDA) is identified, dissected out, and ligated distally to insert and place the catheter in the GDA-hepatic artery junction to decrease the risk of thrombosis. The catheter should be secured with two silk ties and connected to the device located in the subcutaneous pocket created. After finishing this procedure, the catheter should be tested using fluorescein dye or methylene blue to confirm bilobar perfusion and to rule out the presence of extrahepatic perfusion [37].

Postoperative complications are seen in 10–40 % of patients and significantly decrease with the expertise and experience of the surgical team. Allen et al. [41] evaluated the complication rate of HAIP in 544 consecutive patients. One hundred twenty (22 %) patients had at least one complication related to the pump, and the incidence of pump failure increased with the time (first year = 9 %; second year = 16 %). Early complications were usually

related to the hepatic artery system and were frequently salvaged, while late complications were mainly related to the catheter. Complication rates were higher when there was variant arterial anatomy, catheter insertion into another vessel (not the GDA), placement during the first half of a study period, or when the surgeon had less experience (less than 25 procedures). More recently, another study from MSKCC showed that the risk of biliary sclerosis associated with HAIP chemotherapy was very low (5.5 % in patients receiving adjuvant therapy and 2 % in those with unresectable LOD) [42].

Despite multiple drugs being tested via HAIP chemotherapy, floxuridine (FUDR) has been the most common and currently is the standard treatment. This drug has a high extraction rate in the liver [37]. Since most complications of the FUDR affect the liver and/or bile ducts, liver enzymes should be evaluated every 2 weeks to adjust the dose. The use of concomitant dexamethasone has been associated with a lower elevation of bilirubin levels and a higher rate of partial and complete responses [39].

HAIP chemotherapy has been mainly used as *adjuvant therapy* in patients with LOD who have undergone complete resection. Multiple randomized trials have shown a benefit in improving survival in this setting [43–45]. However, this discussion is limited to its role in unresectable disease.

Kemeny et al. [46] enrolled 162 patients and randomized 99 to receive systemic chemotherapy or HAIP with FUDR. Patients with ED or resectable disease were not included in this trial. Forty-eight patients received HAIP chemotherapy and 51 systemic chemotherapy. A significantly better response was observed in patients receiving HAIP chemotherapy (50 vs. 19.6 %, $p = 0.001$). Thirty-one patients initially treated with systemic chemotherapy crossed over to the HAIP treatment. Interestingly, 27 out of 48 (56 %) patients who initially received HAIP chemotherapy developed EHD compared with 19 out of 51 (37 %) patients initially treated with systemic disease ($p = 0.09$). Importantly, 11 out of these 19 (58 %) patients developed EHD when they crossed over to HAIP chemotherapy. Median time of progression in the HAIP group was 9 months and better than in the systemic group (5 months), $p = 0.016$), but liver progression was significantly lower in patients receiving HAIP chemotherapy. Median survival was 17 months in the HAIP group and 12 months in the systemic therapy ($p = 0.4$), but those patients who were initially treated with systemic therapy and crossed over to HAIP chemotherapy had a better survival (18 months) than those who did not cross over (8 months). This study mainly showed that in patients with LOD, HAIP chemotherapy is associated with a better response, but does not decrease the risk of developing EHD, as the natural history of this disease usually shows, and patients could benefit from a combination of local and systemic treatment.

In another prospective trial, Kemeny et al. [38] evaluated the role of systemic chemotherapy combined with HAIP chemotherapy in patients with unresectable LOD. Twenty-one patients received HAIP chemotherapy with FUDR plus systemic oxaliplatin and irinotecan, and 15 patients received HAIP chemotherapy with FUDR plus systemic FOLFOX. Nineteen out of 21 (90 %) patients of the first group had a partial response, 7 (33 %) underwent a liver resection, and 2 did not have residual tumor. Median time for liver and extrahepatic progression was 16.4 and 16.9 months. Median survival was 35.8 months, and 2-year survival was 65 %. Similarly, 13 out of 15 (87 %) patients had a partial response in the second group. Median time for liver and extrahepatic progression was 9.4 and 10.8 months. Median survival was 22 months, and 2-year survival was 40 %. This promising study confirmed that the best response is obtained using a combination of systemic and HAIP chemotherapy, and suggested that the combination of oxaliplatin and irinotecan has the best response. Based on these findings, Kemeny et al. [40] treated 49 patients with unresectable LOD with HAIP chemotherapy plus systemic chemotherapy with oxaliplatin and irinotecan. Twenty-three patients were chemotherapy-naïve at the moment of being included in this study and 90 % had a clinical risk score ≥ 3. Forty-five out of 49 (92 %) patients had a partial (84 %) or complete (8 %) response, and 23 (47 %) patients underwent resection (R0 = 19, 3 with complete response) after a median time of 7 months. Twelve patients required PVE, four patients underwent two-stage surgery, and ten were treated with radiofrequency ablation in addition to surgery, confirming that these patients usually need a complex surgical treatment. Median DFS for patients undergoing resection was 7.6 months, but when all patients were evaluated, median survival was significantly better in patients who were chemotherapy-naïve compared with those who had received chemotherapy previously (50.8 vs. 35 months, $p = 0.02$).

More recently, Ammori et al. [47••] retrospectively evaluated the experience of MSKCC treating patients with unresectable CLM who were treated with systemic and HAIP chemotherapy. This study is important in order to understand the natural history of this group of patients, since most of them were treated outside a protocol. Three hundred seventy-three patients were evaluated between 2000 and 2009. The majority had a clinical risk score ≥ 3, bilobar disease, and ≥ 4 tumors. This study also included 60 (16 %) patients with EHD, but most of them were diagnosed during surgery, and only 18 patients had a previous history of EHD (resected in 14 and anastomotic recurrence in 4). Two hundred ninety-six (79 %) patients had received chemotherapy previously (oxaliplatin = 199, iriniotecan = 121, and bevacizumab = 121). Ninety-two (25 %)

patients converted to complete resection/ablation after a median time of 7.1 months. An exclusive liver resection was performed in 38 (41 %), while 46 (50 %) were treated with resection plus ablation, and 8 (9 %) were only ablated. Sixty-two out of these 92 (67 %) patients recurred after a median time of 16 months, and 14 underwent a new resection/ablation. Median survival for the conversion and non-conversion group was 59 months and 16 months, while 5-year survival was 47 and 6 %, respectively ($p = 0.001$). At the moment of analysis, 38 patients were alive without evidence of disease, and 24 were alive with disease. Multivariate analysis showed that conversion to resection, preoperative CEA < 200 ng/ml, and being chemotherapy-naïve were independent predictors factors of survival.

Unfortunately, there are no randomized trials to define the advantage in terms of survival between HAIP chemotherapy and systemic chemotherapy in patients with unresectable LOD. Most studies are phase II trials that evaluate the rate of response to this combination of treatments. Since the best response was obtained with a combination of systemic and HAIP chemotherapy, including oxaliplatin and irinotecan, it is highly necessary to design and conduct a phase III trial with the aim of defining what is the best treatment to improve survival.

Studies from other institutions have been unable to replicate the excellent results reported by MSKCC. Complication rates in general have been higher. There are a number of potential reasons for this including: institutional expertise, commitment to the protocol and the need for an institutional 'champion,' individual expertise, the medication and dosages used, and ability to salvage and manage complications when they do occur. The external validity of the technology still needs to be confirmed at other expert centers [48].

Directed Radiotherapy

Selective internal radiation (SIR) spheres is a novel treatment that has been used in patients with CLM and unresectable LOD [49]. The microspheres contain $Yttrium^{90}$, which is a high-energy beta-emitting isotope that is embolized through the hepatic artery, delivering 200–300 Gy on average. This method has the advantage of delivering a higher dose to the liver without having liver toxicity compared with external beam radiation, which can only deliver 30–35 Gy to the liver [50]. Small studies have evaluated the role of SIR spheres in unresectable CLM, mainly as third or fourth line of therapy.

Stubbs et al. [49] treated 50 patients with extensive CLM that were not considered for resection or ablation between 1997 and 1999. Each patient underwent an HAI catheter placement through the GDA. Eight (16 %) patients had evidence of minor EHD at the moment of treatment. Despite a CT scan performed 3 months after completing the treatment that showed a reduction in tumor size in 32 patients, 23 (52 %) had developed EHD 6 months after treatment. After a median follow-up of 25.5 months, 37 patients had died of disease, most of them for progression of EHD. Median OS was 9.8 months from treatment.

In another study, Gray et al. [51••] randomized 70 patients with bilobar and unresectable CLM to receive HAIP chemotherapy alone with FUDR or HAIP chemotherapy with FUDR plus SIR-spheres. At the moment of analysis, only four patients were alive. Patients receiving HAIP chemotherapy plus SIR-spheres had significant higher rate of complete or partial response (44 vs. 18 %, $p = 0.01$), changes in tumor volume (50 vs. 24 %, $p = 0.03$), and decrease of CEA levels (72 vs. 47 %, $p = 0.004$). In addition to this, patients treated with both modalities had a higher PFS, but the OS was similar between the groups.

In a separate trial, Lim et al. [52] evaluated 30 patients who were enrolled in three Australian centers. It included patients with unresectable liver metastases previously treated with 5-FU-based chemotherapy. Patients with EHD were included only if the liver was the dominant site of metastasis. A decrease of more than 30 % of the target lesions at 2 months of follow-up defined partial response, while progression of disease was defined as an increase of more than 20 % of the target lesion. All patients had failed 5-FU-based chemotherapy, and 22 (73 %) had failed oxaliplatin/irinotecan regimens. Despite these failures, 21 out of 30 patients receive 5-FU concurrent with SIR-spheres. Partial response was observed in ten patients, but the response continued during the first year, and one patient with initial partial response had complete response at 6 months of treatment. After a median follow-up of 18 months, the median duration of response was 8.3 months. Another 8 patients had stable disease, and 12 progressed. Median PFS was 5.3 months in all patients, and 9.2 months for patients who had achieved a partial response. Four (13 %) patients had severe toxicity, defined by gastric or duodenal ulcers that were managed medically.

More recently, Cianni et al. [53] retrospectively evaluated 41 symptomatic patients who were treated with SIR-spheres between 2005 and 2008. Thirty-nine patients had bilobar metastases, and four (9.7 %) had EHD, involving porta hepatis lymph nodes or bone. All patients had failed the first, second, and third line of chemotherapy. Before starting the treatment, each patient had a complete evaluation of the vascular anatomy of the liver with angiography, and all branches of the hepatic artery to the GI tract were coiled. In a second step, a complete evaluation of possible arteriovenous shunts from the hepatic artery to the pulmonary system or

ectopic implantation into the GI tract was performed. The interval between lobar treatments was 4–6 weeks, and the possibility of re-treatment was evaluated after 8 weeks of completing the initial treatment. Complications related to the procedure were low: five patients presented with mild abdominal pain and nausea after 12 h after procedure, one patient had a medically treated acute cholecystitis 25 days after the procedure, two patients had gastritis 4 and 6 weeks after the procedure, and one patient had liver failure 40 days after the procedure, which was the only major hepatic complication. Eight (4.8 %) patients had complete response, 17 (41.5 %) had partial response, 14 (36.2) had stable disease, and 8 (19.5 %) had progression of disease. At the moment of analysis, ten patients were alive, and the others died because of disease progression. Median OS was 1 year, and median PFS was 0.8 years.

In another study, Hong et al. [54] utilized a different modality of treatment. They included 36 patients with liver dominant CLM treated with chemoembolization (TACE) or Thera-spheres with Yttrium^{90}. Twenty-one patients were treated with TACE, and 15 received Thera-spheres. At the time of analysis, only five patients in the group treated with TACE were alive. Moreover, the follow-up after treatment was too short to make assumptions about survival (6.3 months for TACE and 5.7 months for Thera-spheres). Three patients died before 30 days and had disease progression. The authors reported a median survival from treatment of 7.7 months for the TACE group and 6.9 months for the Thera-spheres group.

Finally, Turkmen et al. [55] evaluated 61 patients with unresectable metastases, and 23 patients had CLM. This study does not describe the response obtained in this subset of patients, but they reported a median OS of 14 months.

In summary, SIR spheres have been mainly used in patients with unresectable and extensive disease who have received other modalities of treatment previously. The impact on survival is poor, and it should be used very selectively.

Conclusions

Patients with unresectable LOD represent the vast majority of individuals with CLM that are evaluated in a hepatobiliary unit. Many of them will not have a good response to systemic and/or local treatments and will progress and die from their disease. On the other hand, a small and highly selected subgroup of patients (12.5–20 %) will have enough response in the liver to achieve surgical exploration and eventually complete resection. Unfortunately, most patients treated with complete resection will recur at a median time of 12 months and will need consideration for repeat resection or other therapy. Most studies are retrospective or small phase II trials that have been conducted to determine the rate of response to local and/or systemic treatments. The lack of well-conducted phase III trials does not allow us to define either the standard treatment or the impact on survival of current therapies for most of these patients. In addition, it has been difficult to replicate these results at some expert centers. Thus, it is necessary to develop a multicenter phase III trial including both systemic and local treatments. Since the combination of three systemic drugs (FOLFOXIRI) associated with HAIP chemotherapy is the treatment that has shown the best response into and outside the liver in phase II trials; a phase III trial including two arms, FOLFOXIRI versus FOLFOXIRI plus HAIP chemotherapy, is needed not only to define the best treatment, but also to define the impact of all these therapies on survival.

Compliance with Ethics Guidelines

Conflict of Interest Jean M. Butte, Chad G. Ball, and Elijah Dixon declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Recently published papers of particular interest have been highlighted as:
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