Abstract. Liver metastasis is the most common site of colorectal cancer (CRC) metastasis. Approximately half of all colorectal cancer patients will develop liver metastases. Although radical surgery is the standard treatment modality, only 10-20% of patients are deemed eligible for resection. Despite advances in survival with chemotherapy, surgical resection is still considered the only curative option for patients with liver metastases. Much effort has been expended to address patients with metastatic liver disease. The majority of evidence stated a significant survival benefit with surgical resection to reach an overall 5-year survival rate of 35-55% after hepatic resection. However, still majority of patients will experience disease recurrence even after a successful resection. In this review, we describe current status and controversies related to treatment options for CRC liver metastases and its potential for enhancing oncologic outcomes and improving quality of life.

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1. Introduction

Worldwide, colorectal cancer (CRC) has become the third-most common type of malignancy and fourth-most frequent cause of cancer-related mortality. The CRC metastasis rate has increased steadily to 20-25% (1-4), and 70-80% of these cases occur in the liver (5). Almost half of all patients who undergo resection for primary CRC will eventually develop metachronous liver metastases (6), the leading cause of death in this population with a median overall survival (OS) duration of 6-12 months if left untreated (7). Surgical resection is the mainstay of treatment for colorectal liver metastasis (CRCLM); however, liver metastases are deemed resectable in only 10-20% of cases (8) with disappointing results and high recurrence rate. One multi-center study of 1669 patients found that more than half developed recurrences, with median disease-free survival duration of 16.3 months (9).

Therefore, various alternative options for CRCLM management have been extensively studied. However, definition debates add serious strain in designing management plan. Particularly in resection for cure was very low in synchronous compared to metachronous, however, new chemotherapy agent has a role to improve resection rate up to 30-40% (5). Definition of synchronous metastases is still debated, although it has been highly suspected in those detected up to 3 (10), 4 (11), or 6 months (12,13) after the primary diagnosis.

Noteworthy, multidisciplinary team decision-making and evolving chemotherapy agents and patient care are contributed to improve 5-year OS rates from <8% to 25-40% (14,15). Neoadjuvant treatment, which is used for local tumor amelioration, has a high response rate (>50%) and can increase the rate of resectability from 10 to 30% (16,17), although the recurrence rate still remains high, with OS not exceeding 3 years (18). Therefore, alternative treatment strategies are essential. We reviewed current data and analyzed existing treatment modalities. We hope this review will generate prospective insights into ongoing controversies regarding the management of liver metastases of CRC.
2. CRC liver metastasis treatment challenges: What are the limitations of liver resection?

Generally, liver metastasis can manifest in both synchronous or metachronous forms. These presentations raise questions regarding the ability to resect the primary tumor, liver metastasis, or both and when to consider different forms of radiotherapy with or without chemotherapy. In the following section, management of synchronous CRCLM will be elaborated in details.

Synchronous resectable CRCLM
Extent of liver resection. Liver resection is the only potentially curative treatment for CRCLM (19). The major concern involves the achievement of R0 resection without consequent complications, particularly the avoidance of an insufficient future liver remnant (FLR) during major hepatectomy. Decision to estimate FLR is left for surgeon decision that depends mainly in the status of the liver preoperatively. For instance; resection up to 75% is adequate in normal liver, however patients with chronic liver disease but without cirrhosis usually require an FLR of at least 30% while patients with cirrhosis but without portal hypertension require an FLR of at least 40% (20, 21).

Dam et al (22) compared limited (criteria: <3 unilateral, non-centrally located liver metastases, no extrahepatic metastases) and extended hepatectomy in 298 patients with CRCLM. Patients who underwent limited resection had a lower complication rate (19.5% vs. 33.1%, P<0.01), longer OS duration (68.8 months vs. 41.4 months, P<0.001), and longer median disease-free survival (DFS; 22.0 months vs. 10.2 months), compared with the extended group. Based on these criteria, only 15-20% of CRCLMs will be suitable for resection. Recent advances in chemotherapy have increased the indications of liver resection. Accordingly, all of the previous criteria have been largely abandoned (23, 24). Patients with stable health, ≤4 lesions, bilateral metastases, no extrahepatic metastases, and adequate FLR are considered resectable and may achieve 5-year DFS and OS rates of 21.5 and 50.9%, respectively (25, 26).

In addition, addressing management of extra-hepatic metastasis (EHM) along with CRCLM is challenging and may end with dismal outcome; however, surgical intervention can improve OS in resectable cases. What to do and when to consider resection? We could estimate the current inquiry from the results of an international multi-institutional analysis (27) involving 1629 patients who underwent resection of CRCLM found that most patients had solitary EHM, and the 5-year survival rates were 26 and 58% for those with and without EHM, respectively (P<0.01). In addition, EHM characteristics such as R1 margin positivity, multiple sites, and location were associated with worse survival. Accordingly, EHM resection is possible in selected patients without presence of extensive disease.

The selection criteria for liver resection are essential in order to avoid an inadequate FLR, a major cause of surgery-related death. Normally, patients can survive with only 20% of a healthy normal liver. However, for patients whose livers are affected by chemotherapy or who expect to receive postoperative chemotherapy, 30-40% of the liver should be preserved (28, 29). Liver resection is planned if a complete R0 resection is feasible, at least 2 liver segments with independent inflow and outflow are spared, and appropriate biliary drainage is maintained.

Management options in resectable CRCLM, surgery or chemotherapy first? The choice to administer initial surgical or chemotherapeutic treatment remains a subject of debate. However, upfront liver metastasis resection is the primary treatment modality for resectable CRCLM (rCRCLM) (30-32), however, most of such cases presented with a higher recurrence rate (33). Therefore, the National Comprehensive Cancer Network (NCCN) recommends 6 months of perioperative systemic chemotherapy. However, standard policy and treatment strategy are poorly defined (34). Currently, alternative treatment has been tried and introduced radiofrequency ablation (RFA) in resectable CRCLM, which has failed to generate good results. A recent meta-analysis (35) agreed with this fact, they investigated the role of RFA vs. resection for rCRCLM and found that the former was associated with poorer OS (hazard ratio (HR): 1.85, 95% confidence interval (CI): 1.48-2.32, P<0.00001) and DFS (HR: 1.68, 95% CI: 1.14-2.48, P=0.009).

Thereafter, neoadjuvant chemotherapy has been proposed to assess tumor biology, at which chemotherapy could be prolonged and surgery would be delayed in poor responders until good response was shown (36, 37). Adam et al (38), enrolled 131 patients with rCRCLM found worse 5-year survival in poor responders compared to stable or responsive disease (8% vs. 30%, 37%; P=0.0001), respectively. Moreover, Ruenberger et al (39) conducted a prospective trial to assess the efficacy of 6 cycles of neoadjuvant XELOX or FOLFOX4 in 50 patients with rCRCLM demonstrating recurrence-free survival rates correlated with tumor responses (24.7, 8.2, and 3.0 months) in responsive, stable, and progressive disease, respectively. Based on these results, perioperative chemotherapy upfront could be an essential par to assess tumor response, which is supported by EORTC 40983 studies (16). However, these studies reported chemotherapy-associated liver damage and a significantly higher rate of postoperative complications with chemotherapy than with surgery alone (25% vs. 16%). Therefore, chemotherapy may cause liver injury and poor short-term prognosis consequently (40). Other studies including those of EORTC 40983 found an association between high morbidity rate and the number of chemotherapy cycles (17, 41, 42), suggested that a period of 3 months preoperative FOLFOX-4 chemotherapy should not be exceed in order to avoid chemotherapy-related liver toxicity (39).

A very recent systematic review from 2016 (43), summarized four well-organized trials addressing the role of chemotherapy to rCRCLM. Two trials demonstrated significant improvements in DFS with combined chemotherapy and surgery, compared to surgery alone. FOLFOX, along with liver resection, yielded improvements in DFS, compared to surgery alone. In addition, a new EPOC randomized controlled trial (44), posted encouraging results regarding the addition of the molecular target agent cetuximab to chemotherapy for operable CRCLM. Progression-free survival (PFS) was significantly shorter with cetuximab than with chemotherapy alone (14.1 vs. 20.5 months, respectively). OS, however, remains under investigation. Discrepancies in the reported survival benefits with neoadjuvant chemotherapy remain under debate, as illustrated in Table I.
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Surgical approaches for liver metastasis. Several liver resection techniques exist. Previously, two-stage hepatectomy (TSH) was recommended to reduce surgical trauma (45). However, most cancer centers, including our institution, supported a single-stage approach after finding insignificant morbidity during perioperative management (46,47). However, no existing protocol favor simultaneous resection over a staged approach. The approach depends on the surgeon's experience and patient's physical status. The only possible advantage of single stage over two-stage procedure is the earlier initiation of adjuvant chemotherapy (48). Silberhumer et al (49) studied 429 patients subjected to operative treatment for CRC with simultaneous liver metastases; 75 and 25% underwent simultaneous and staged resection, respectively. The 1-year survival rates were 90.5% in the simultaneous group and 92.6% in the staged group, and the corresponding 5-year survival rates were 38.5 and 38.9%, respectively. Simultaneous liver resection and staged procedures are associated with similar long-term cancer outcomes. We encourage single-stage liver resection together with primary lesion resection whenever possible, as shown in Fig. 1.

Moreover, radical extended lymph node dissection should be considered for suspected lymph nodes in the hepatic pedicle or in patients with >3 poorly differentiated metastatic lesions in segments (IV and V) (50). Currently, TSH is considered only if an adequate liver remnant cannot be preserved after HR; TSH and HR; In this case, certain groups of liver tumors are resected first, followed by resection of the remaining tumors in a second procedure after a liver regeneration period (4-12 months) (51). The two-stage procedure is largely used for unresectable liver metastasis or to render unresectable lesions resectable, especially when combined with alternative treatments such as portal vein embolization or RFA (discussed in detail later on).

3. Synchronous unresectable CRCLM (uCRCLM)

This common scenario presents a real challenge in the medical field. Whether primary mass resected first to debulk tumor-related complications or upfront chemotherapy should be administered first to downstage the tumor. Numerous treatment procedures are tailored according to the patient's presentation and tumor criteria as follows:

Evolution of chemotherapy in CRCLM. Upfront chemotherapy is the treatment modality of choice for uCRCLM. Appropriate chemotherapy regimen promote tumor downstaging and

<table>
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<tr>
<th>Table I. Chemotherapy trials in resectable CRCLM.</th>
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<td>Study</td>
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<tr>
<td>Primrose et al (44, EPOC)</td>
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<td>Nordlinger et al (122)</td>
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<td>Ychou et al (123)</td>
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<td>Portier et al (50)</td>
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DFS, disease-free survival; FOLFIRI, fluorouracil, leucovorin, irinotecan; LV/5FU, folinic acid (leucovorin)/5-fluorouracil; MCT, muticentric trial; OS, overall survival; PFS, progression-free survival; rCRCLM, resectable colorectal cancer liver metastasis; RCT, randomized controlled trials; wt, wild-type; FOLFOX, 5-FU, lecovorin, oxaliplatin.

Figure 1. Simultaneous liver and primary resection in a challenging tumor location. Liver metastasis located intra-parenchyma and near portal vein has been resected completely without consequent complications.
can subsequently render unresectable tumors into resectable (i.e., conversion chemotherapy) (52,53). Previously, single-agent chemotherapy with 5FU and folinic acid (5FU/LV) yielded a response of 20%. A randomized trial (54), allocated 40 patients to receive 5FU/LV or placebo, marked improved OS was observed with chemotherapy, compared with placebo (11 months vs. 5 months). Consequently, combined therapy composed of 5FU and oxaliplatin or irinotecan treatment has increased response rates to 40-50%, with estimated median OS durations of 12-20 months (55,56).

Several recent publications have described well-designed phase III trials that evaluated the benefits of oxaliplatin-based chemotherapy particularly in improving pathological response rates (57-61). This conclusion was investigated in a recent meta-analysis by An et al (62), and it confirmed the benefits of oxaliplatin for local and distant metastasis. Furthermore, Zakaria et al (52) examined the application of three chemotherapy agents and tumor responses in 42 patients with uCRCLM; 60% achieved tumor reduction, 40% underwent surgery, and the median survival duration was 26 months. However, a high postoperative recurrence rate was observed (73%). Overall, a combined approach with resection yielded higher resectability rates and higher negative margins for uCRCLM (63,64).

The GERCOR study (65), randomly allocated 109 patients with CRCLM to FOLFIRI as a first-line therapy followed by FOLFOX6; 111 additional patients were assigned to receive FOLFOX6 followed by FOLFIRI. The median survival was equivalent in both arms (21.5 vs. 20 months, respectively). However, in FOLFOX arm, 22% of patients received surgery for liver metastases vs. 9% in the FOLFIRI arm (P=0.02). A phase III trial of 5FU/LV, irinotecan, and oxaliplatin (FOLFIRINOX) indicated an effectively better response but high toxicity (grade 3/4 neutropenia); accordingly, this approach warrants further monitoring (66). We recommend single stage resection in rCRCLM whenever is possible or upfront chemotherapy to assess tumor biology and response in borderline resectability of liver metastasis.

Emerging target agents in liver metastasis. Molecular target agents specific for vascular endothelial growth factor (VEGF) have been developed, including bevacizumab and cetuximab. Saltz et al (67), evaluated the efficacy of adding bevacizumab to oxaliplatin-based chemotherapy [capecitabine plus oxaliplatin (XELOX) or (FOLFOX-4)] in 1401 patients with CRCLM. The median PFS durations were 9.4 months in the bevacizumab group and 8.0 months in the placebo group (P=0.0023); the groups had similar OS and response rates. In another randomized trial conducted by Bokemeyer et al (68), to evaluate the addition of cetuximab to FOLFOX-4 vs. FOLFOX-4 only, cetuximab was associated with a clinically significant increase in overall response (61% vs. 37%; P=0.01) and reduced risk of disease progression (hazard ratio=0.57; P=0.0163) when compared with FOLFOX-4 alone, particularly in KRAS wild-type tumors. Based on these data, we encourage the FOLFOX regimen, in addition to target agents, as a first-line treatment of choice at our institute. Our recent report by Kim et al (69) reviewed 50 patients with locally advanced rectal cancer and borderline-resectable liver metastases. Patients were treated by short-course radiotherapy (SCRT) and upfront chemotherapy (FOLFOX, FOLFIRI, +/- target agent), with delayed surgery. Tumor downstaging and R0 resection were achieved in 35 (70%) patients. The median PFS was 16 months, and the 2-year PFS rate was 34.8%. Furthermore, chemotherapy can be administered via hepatic arterial infusion (HAI), which yields higher response rates to both first and second-line therapies particularly in oxaliplatin or irinotecan infusion (70,71). Nevertheless, HAI is a technically demanding procedure that should be handled by experts.

Radiotherapy application in CRCLM. Systemic chemotherapy has been widely studied; however, the oncologic outcomes are inconclusive in CRCLM (73). Therefore, current questions are raised whether the radiotherapy dose or pathway could contribute to achieving better results is controversial. A phase II trial (69) evaluated a 12-week FOLFOX regimen with pelvic CRT in 26 patients with symptomatic advanced rectal cancer and metastatic disease. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) revealed metabolic response rates of 96% for primary rectal cancer and 60% for metastatic disease; evidence of good pathological responses was also observed in resected specimens. Of note, the authors of that study invented a new approach at which RT therapy was divided into 2 courses to reduce toxicity. Accordingly, 92% of the 26 patients reached treatment week 11 without deviation, suggesting positive outcomes of this treatment strategy. The RT formats and strategies will be discussed in the following sections.

Application of SCRT in locally advanced rectal cancer with uCRCLM. Application of radiotherapy has widely been used in the field of CRC. In CRCLM, however, SCRT has been proposed along with chemotherapy and delayed surgery, which has yielded a great improvement in controlling the tumor locally. Technique and procedure of SCRT has been previously described in our study (74). Besides, combined approaches of SCRT along with FOLFOX have been validated in several recent studies.

van Dijk et al (4) evaluated SCRT followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin chemotherapy in 50 patients with CRC metastases. Of these 36 (72%) patients could undergo surgery. The 2-year OS rate was 80%. Recently, we proposed a phase II trial (74) of 6 patients diagnosed with uCRCLM and locally advanced rectal cancer. This trial was designed to assess upfront treatment with FOLFOX and SCRT (25 Gy/5 fractions), followed by surgery after a 4-6-week delay. We observed regression of most metastatic lesions and simultaneous rectal tumor downsizing, thus one stage procedure was feasible. Radu et al (75), in accordance with our study conclusion, in 46 patients with unresectable rectal cancer, with or without metastases, received SCRT with delayed surgery. Thirty-seven (80%) patients ultimately underwent surgery, and 32 (86%) achieved R0 resection.

In addition, Yoon et al (76), reported our experience of SCRT in 50 patient diagnosed with locally advanced rectal cancer and synchronous liver metastasis, receiving chemotherapy and
delayed surgery. Of these patients, 35 underwent radical surgery for primary and metastatic tumors to achieve therapeutic resection; 13.6% achieved clinical complete response (CR) of metastases. PFS was longer in the curable group. The 2-year PFS rate was 34.8%. The 2- and 5-year OS rates were 73.9 and 55.1%, respectively. This approach could be an alternative treatment modality in locally advanced rectal cancer with liver metastasis that require further investigation in appropriate clinical trial in the future. Several studies have addressed this aspect and are illustrated in Table II.

4. Ablative modalities for liver metastasis

Liver metastases are best eradicated by excision; however, if resection is unsuitable, consensus suggests that combination ablative therapy should be considered to prevent liver failure after major resection. RFA, cryotherapy, or high intensity focused ultrasound, can be used in combination to offer curative treatment in patients with unresectable tumors (77,78). Currently, a phase II randomized extension of the EORTC intergroup randomized study 40004 (CLOCC) (10) has enrolled 119 patients with uCRCLM to investigate the benefit of FOLFOX plus RFA vs. FOLFOX alone. The inclusion criterion was a maximum of 9 liver lesions without extrahepatic involvement. The 30-month OS rates were 61.7% in the combination group vs. 57.6% in the control group. The median OS durations were 45.6 vs. 40.5 months (P<0.01), thus favoring combination treatment over FOLFOX alone. Abdalla et al (79) reported their experience with RFA vs. chemotherapy alone for CRCLM; the authors observed significant improvements with RFA relative to chemotherapy alone.

Furthermore, combined therapy (resection+RFA) help to achieve a R0 status while maintaining an adequate FLR to avoid postoperative hepatic failure (80). However, surgical decision for RFA should be crucial and tailored accordingly, otherwise may end with unwanted consensus in particular of higher local recurrence rate. Qui et al (81) enrolled 112 patients diagnosed with unresectable liver metastasis from different primary tumors. The ablation success rates were 93.3% for hepatocellular carcinoma (HCC) and 96.7% for secondary liver metastasis. The corresponding 5-year overall recurrence rates of these diseases were 80 and 77.8%, respectively. Park et al (82) predicted factors associated with high recurrence rates after RFA in patients with hepatic metastases. Lesions with ablative margins of ≥5 mm were associated with longer disease-free interval than lesions of <5 mm. These finding are on line with our experience. Hur et al (83) conducted comparative study between HR and RFA in 67 consecutive patients with solitary CRCLM. Forty-two patients underwent HR and 25 patients underwent RFA. The 5-year overall and local recurrence-free survival rates (LRFS) were in favor of HR (50.1 and 89.7%, respectively) and (25.5 and 69.7%, respectively) than RFA, particularly in patients with tumor size >3 cm. However, LRFS was likewise to resection with tumor size <3 cm (95.7% vs. 85.6%, P=0.304). Thus, we recommend selecting appropriate patients and tumor character ahead of planning RFA procedure.

Noteworthy, Mima et al (84) evaluated combined therapy (RFA, hepatic resection HR in patients previously received chemotheraphy (FOLFOX±bevacizumab) vs. HR alone in a total of 118 patients with uCRCLM. The postoperative morbidity rates were 17 and 23%, respectively (P=0.640). Local recurrence at the RFA site occurred in only one tumor (1.6% per lesion, 7.7% per patients). The 3-year PFS rates were 45.3% in the HR group and 12.8% in the HR+RFA group (P=0.472). The 3-year OS rates were 70.4% in the HR group and 77.1%
in the HR+RFA group (P=0.627). These data suggest that in patients previously treated with chemotherapy, a combined approach (RFA+HR) effectively reduces the recurrence rate if used appropriately. Nevertheless, these studies were retrospective, and a randomized controlled trial is needed to delineate the risks and benefits of particular approaches in uCRCLM.

Orientation of RFA limitation and complication is crucial. Berber et al (85) suggested criteria for the prediction of a poor response to RFA treatment; >3 liver metastases, a carcinoma-bryonic antigen (CEA) level >200 ng/ml, extrahepatic disease, and liver metastasis >5 cm. In addition, RFA is associated with few complications (e.g., bleeding, infection, bile duct injury) and a stably high local recurrence rate (estimation: 40%), particularly if performed via percutaneous approach (86). Therefore, intraoperative RFA is an effective and preferred method, although technical precautions are highly warranted. A meta-analysis advocated safety of RFA in liver tumors <3 cm in size that may yield lower recurrent rate (87). The lack of well-designed trials currently inhibits comparisons with various other treatment modalities (88). RFA remains an attractive alternative to major HR with both curative and palliative intent, and yields promising results after taking strict precautions for lesions near major biliary or vascular structures (89).

5. Portal vein embolization (PVE)

The goal of portal vein embolization (PVE) is to achieve complete portal occlusion of the targeted segments and generate adequate liver hypertrophy prior to a proposed surgery. Preoperative PVE was first described by Elias et al (90) in 14 patients with hilar cholangiocarcinoma, in whom successful results were achieved without major consequences. The Cardiovascular and Interventional Radiological Society of Europe (CIRSE) reported minor and major complications of PVE at 25 and 5%, respectively (91). However, PVE contraindications should be noted; these include extensive ipsilateral tumor thrombus and clinically evident portal hypertension. However, PVE may be an important component of two-stage hepatectomy, thus rendering unresectable bilateral CRCLM resectable (92,93). Narita et al (94) studied the outcomes of PVE in 80 patients with liver metastasis, among whom 61 had completed two-stage hepatectomy. The 5-year OS rate was 32%, and the median OS duration was 39.6 months.

A major drawback of PVE is the risk of tumor growth after embolization, as observed in a previous large observational study. The authors assessed the effects of PVE and bevacizumab on liver hypertrophy and tumor growth to control group (bevacizumab without PVE). Among 119 study patients, significant increases in total tumor volume were observed in the PVE group, whereas decreases were observed in the control arm (0.07 vs. 0.06 cm³/day, P<0.01) (95). An animal study by Maggiori et al (96) found that PVE increased tumor growth in the non-occluded liver while decreasing growth in the occluded liver. This tumor growth after PVE was poorly understood, but might be attributable to post-PVE proliferative activity involving increased levels of cytokines and inflammatory mediators (97). Therefore, does PVE jeopardize the downstaging effect of chemotherapy on CRCLM? This debate has not been defined yet. Noteworthy, hepatocyte growth factor (HGF) has been suggested as the major liver and tumor stimulus, as reported by Zou et al (98). Thereafter using of anti-inflammatory medication to ameliorate PVE proliferative activity is a topic of debates.

Emerging of Selective internal radiotherapy (SIRT) contributed to develop the PVE technique. In a meta-analysis (99), SIRT exhibited appropriate usefulness in 90% of uCRCLM cases. Therefore, a combination of PVE and SIRT could provide a surrogate for major hepatectomy (SIRT will be explained later in this review). However, this combination has not yet been established (100). Remaining controversies surrounding challenges and treatment options suggest that considerable effort will be required in the future to validate the PVE treatment.

6. Emerging techniques in addressing uCRCLM

Associating liver partition with PVL for staged hepatectomy (ALPPS). Schnitzbauer et al (101) described a novel approach: associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). This new surgery resulted in a 74% increase in the volume of the liver remnant in a mean period of 9 days. However, this procedure was associated with a morbidity rate as high as 68% and a mortality rate as high as 14%. From a technical point of view, standard ALPPS, briefly, has two stages; stage I includes right portal vein ligation (PVL), and in situ splitting of the liver parenchyma along the right side of the falciform ligament. All portals, arterial, and biliary duct of segment IV are identified and divided. Biliary and arterial structures and venous drainage of the right liver are retained. Stage II elected after 1-2 weeks to address targeted plan of right-extended lobectomy and ligating of right hepatic artery, right bile duct, and hepatic vein (101). Procedure illustrated in Fig. 2. Moreover, Gauzolino et al (102) described 3 modified forms of the original ALPPS procedure which are out of our score in this review.

Theory of ALPPS. Honjo et al (103) was the first to introduce PVL similar to those of PVE principles. These methods have been compared with regard to FLR hypertrophy; however, the results were inconclusive (104,105). Recently, a novel two-stage liver resection technique emerged that involves a combination of PVL and ALPPS. ALPPS has been designated superior because it is associated with a rapid, abrupt achievement of FLR hypertrophy (80% more rapid than PVL or PVE) thus allowing second-stage surgery within 2 weeks (106). This gain in time allows more rapid liver regeneration and a reduced risk of subsequent tumor growth (101).

Trials of ALPPS for CRCLM. ALPPS has enabled to rescue patients with uCRCLM who have failed to achieve adequate FLR after PVE. Nevertheless, this procedure is technically demanding and associated with a high comorbidity rate (40%) (107). To date, a systemic review and meta-analysis (108) has evaluated three procedures for the treatment of liver tumors: ALPPS, PVE, and PVL. The authors found no significant difference between PVE and PVL in terms of tumor progression or resection rate, whereas ALPPS was associated with a significant increase in FLR. In a 2015 meta-analysis,
Sun et al (109) reported a higher morbidity rate with ALPPS compared with 2-stage hepatectomy (56.3% vs. 36.1%, P<0.01), and a higher resection rate with ALPPS (100% vs. 79.1%). Schadde et al (106) conducted a multicenter study of 320 patients at 55 centers. The reported 75% mortality rate was attributed to liver failure. Accordingly, appropriate selection for ALPPS is crucial.

Surprisingly, authors argue about the true volume of the FLR following the ALPPS procedure. Tissue edema and inflammatory reactions could affect the post-ALPPS liver volume.

Table III. Results of new techniques in treating liver metastasis.

<table>
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<tr>
<th>Authors</th>
<th>Year</th>
<th>No. (study)</th>
<th>Country</th>
<th>Method</th>
<th>Outcome</th>
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<td><strong>SIRT based results</strong></td>
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<tr>
<td>Turkmen et al (127)</td>
<td>2013</td>
<td>61 (RS)</td>
<td></td>
<td>SIRT in liver mets from different primaries</td>
<td>OS responder (32.0±5.6) Non-responder (11.4±2.1), (P=0.054)</td>
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<tr>
<td>Kucuk et al (128)</td>
<td>2011</td>
<td>78 (RS)</td>
<td></td>
<td>SIRT in liver mets from different primaries</td>
<td>55% responder improve PFS</td>
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<td><strong>ALPPS based results</strong></td>
<td></td>
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<tr>
<td>Björnsson et al (129)</td>
<td>2016</td>
<td>23 (RS)</td>
<td>Sweden</td>
<td>ALPPS</td>
<td>Severe complications occurred in 13.6% One (4.5%) patient died, 2 year OS was 59%</td>
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<td>Kremer et al (130)</td>
<td>2015</td>
<td>19 (RS)</td>
<td>Germany</td>
<td>(CTx+ALPPS) vs. ALPPS</td>
<td>Increased FLR volume in non-CTx (98±35%) Increased FLR volume in CTx (59±22%), (P=0.027) CTx impaired FLR hypertrophy</td>
</tr>
<tr>
<td>Torres et al (131)</td>
<td>2013</td>
<td>39 (RS)</td>
<td>Portugal</td>
<td>ALPPS</td>
<td>Left lateral segment of the liver increased 83% Morbidity 59, Mortality 12.8%</td>
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</table>

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; CTx, chemotherapy; FLR, future liver remnant; SIRT, selective internal radiotherapy; OS, overall survival; PFS, progressive-free survival; RS, retrospective study.
size, leading to an over measurement relative to the actual total volume of the FLR (110). The recent technique of hepatobiliary scintigraphy can be used to assess total and regional liver function (111,112). Finally, the ALPPS procedure is in an early milestone stage and is associated with a higher morbidity rate than other treatment modalities; however, the results remain controversial (113). Notably, the mortality rate associated with ALPPS was 9%, but this decreased to 5% in a sub-analysis of patients aged <60 years who were diagnosed with CRCLM (106). We conclude that ALPPS surgery should be strongly considered, as it yields good outcomes in a subset of patients; however, further evaluation through well-organized trials is required in the future.

7. Selective internal radiotherapy (SIRT)

Currently, the new modality for targeting liver lesions emerged in a form of selective internal radiotherapy (SIRT) technique in order to target distal tumor vasculature. Yttrium-microspheres are used for radiotherapy embolization with high energy and parenchyma penetration of >11 mm, which make it effective in liver metastasis trapped at the distal end of tumor vasculature. SIRT, has been previously shown to yield early successes in patients with HCC (114). Since then, other authors have investigated the applications of SIRT for liver metastasis, regardless of primary tumor, and have obtained good results (115,116). Accordingly, SIRT has been assigned as the treatment of choice for 90% of uCRCLMs that achieved success after a chemotherapy failure (99,115). Van Hazel et al (117) conducted a randomized clinical trial evaluating the utility of SIRT plus chemotherapy (FU/LV) vs. chemotherapy alone in 11 patients with uCRCLM. The time to disease progression analysis favored the SIRT arm (18.6 months vs. 3.6 months, P<0.0005). Additionally, the median survival duration was significantly longer in the SIRT arm (29.4 months vs. 12.8 months, P=0.02).

Noteworthy, in 2016, the novel SIRFLOX trial, conducted by Van Hazel et al (118), assessed the efficacy of SIRT plus mFOLFOX6 plus or minus bevacizumab vs. mFOLFOX6 alone. The authors enrolled 530 patients who were stratified into control (263 patients) and SIRT arms (267 patients). No significant improvement in PFS was observed at any site (control, 10.2 vs. SIRT, 10.7 months); however, SIRT significantly delayed disease progression in the liver only (control, 12.6 vs. SIRT, 20.5 months). The complete response rates were 6% in the SIRT arm vs. 1.9% in the control arm (P=0.020). According to the GERCOR database, the response rate was higher among patients with liver-limited metastases, compared to those with extrahepatic metastases (119).

Despite the promising results of SIRT in CRCLM (120), understanding technical principle is essential to avoid inevitable complication. Particularly if there was vascular variation of gastroduodenal artery, left gastric artery or presence of arteriovenous fistula that may transmit radiotherapy to forgut or adjacent structure end with serious radiotherapy damage (121). Thus, orientation about vasculature anatomy before initiating SIRT procedure is a crucial point.

Therefore, SIRT is technically demanding, and certain levels of skill and experience are warranted before planning treatment with this procedure. Therefore, SIRT remains in an early milestone stage, and more effort is needed to validate its safety and feasibility in CRCLM. The results of recent trials are listed in Table III.

8. Conclusion

Although considerable effort has been expended to improve the outcomes of CRCLM, treatment policies are poorly defined. For resectable CRCLM, systemic chemotherapy regimens, together with liver resection, appear to improve DFS when compared with surgery alone. The OS outcomes, however, have not previously been well illustrated. For uCRCLM, several techniques intended to increase the rate of liver resection have emerged. Still, contradictory data and variable results have contributed to an inability to determine an appropriate conclusion. Furthermore, SIRT and ALPPS procedures are demanding in terms of technical skill and resources, but have yielded promising initial results. Much effort remains with regard to achieving satisfactory treatment strategies in CRCLM.

References


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